FOGSI - ICOG
Good Clinical Practice Recommendations
GCPR

Blood Transfusion in Obstetrics and Gynecology

Convenor – Surekha Tayade Co-Convenor – Pratik Tambe

Mentors – Hrishikesh D Pai, Madhuri Patel, Laxmi Shrikhande

Advisors – Sanjay Gupte, Hema Divakar

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Clinical Research Committee

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Disclaimer: These recommendations for "Blood Transfusion in Obstetrics and Gynecology" have been developed, to be of assistance to obstetricians, gynecologists, consulting physicians, and general practitioners by providing guidance and recommendations for managing women with anemia and suffering from hemorrhagic conditions. The recommendations included here should not be viewed as being exclusive of other concepts or as covering all legitimate strategies. The suggestions made here are not meant to dictate how a particular patient should be treated because they neither set a standard of care nor do they guarantee a particular result. To diagnose patients, choose dosages, and provide the best care possible while also taking the necessary safety precautions, clinicians must rely on their own experience and knowledge. The writers or contributors disclaim all responsibility for any harm and/or damage to people or property resulting from the use or operation of any techniques, goods, guidelines, or ideas presented in this content.

BACKGROUND AND EPIDEMIOLOGY

Blood transfusion is the process of transferring blood products into an individual's circulation intravenously.[1] For a number of medical disorders, transfusions are performed to replenish lost blood components. While whole blood was utilized in early transfusions, modern medicine frequently uses blood components such as red blood cells, white blood cells, plasma, clotting factors, and platelets. Maternal mortality is still mostly caused by obstetric hemorrhage, with rates ranging from 13% in developed nations to about 34% in developing nations.[2] An obsetric hemorrhage may occur before or after delivery, but >80% of events occur in postpartum period and are responsible for 25% of the estimated 358,000 maternal deaths each year.[3] Other causes, such as placenta previa, placental abruption, ectopic pregnancy, molar pregnancy, severe nutritional anemia, hemolytic anemias, etc. may also require transfusion therapy. Blood transfusion is an essetial component of emergency obstetric care and appropriate blood transfusion significantly reduces maternal mortality. While indications for transfusion in obstetrics may be emergent as well as nonemergent, the keystone of transfusion practice is that it should be appropriate. The use of blood transfusion is frequently criticized as being "too little, too late" in retrospective analyses of clinical scenarios. On the other hand, various gynecological disorders, such as fibroid uterus, uterine or cervical cancers, operative procedures and dysfunctional bleeding, etc. may lead to anemic status and require blood and component transfusion in women. Surgical procedures in gynecology requires optimization of hemoglobin prior to embarking on the procedure. Although a blood transusion may save life, certain risks involved have to be considered. Rarely, recipients may experience immunological side effects like red cell alloimmunization or spread of infection by transfusion, thus appropriate care has to be exercised. Transfusion guidelines have been designed by various organizations in various countries. While the basic tenets remain the same, certain aspects may change in view of local context.

Intent: The guidelines are a reference of recommended care and are not an endpoint of clinical care. The guidelines are subject to evolution with advances in scientific knowledge and technology.

PURPOSE AND SCOPE

The purpose of this document is to update key concepts related to blood and component transfusion for disorders of women's health and especially related to pregnancy hemorrhage and give clear and precise tools to health personnel in low- and middle-income countries (LMICs) to perform evidence-based management, with the aim of reducing related morbidity and mortality.

TARGETED AUDIENCE

Obstetricians, gynecologists, midwives, nurses, general practitioners, and other health personnel in charge of the care of women, especially suffering from hemorrhage or low hematocrit.

Methodology

These good clinical practice recommendations (GCPR), given by the Federation of Obstetric and Gynaecological Societies of India (FOGSI), followed the process mentioned in the Royal College of Obstetricians and Gynaecologists (RCOG) "Guideline for guideline development - 2020". The topic was selected and approved and a task force was formulated. The core group was identified and the timelines were discussed and communicated. The scope of the guideline was drafted, objectives were framed, and the stakeholders were listed and incorporated in the scope. A systematic review of the literature was

conducted to provide the best possible evidence base for the GCPR. Existing guidelines, meta-analyses, systematic reviews, and key articles relating to blood transfusion were reviewed by the core group and recommendations relevant to the Indian scenario were framed. These recommendations review the available evidences in the field by the members of the task force which include eminent obstetricians, gynecologists, and transfusion specialists of repute. The guideline was peer reviewed by experts, multiple times, and feedback was incorporated. No conflict of interest and good standing was appropriately expressed by all concerned for professional personal or nonpersonal interest, either financial or nonfinancial. The committee evaluated recommendations and evidence using the methodology of the United States Preventive Service Task Force (USPSTF), on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms).

LEVELS OF EVIDENCE

Level of Evidence	*Recommendation*	*Description*
Level 1	Strongly Recommended	Data derived from multiple randomized trials or meta-analyses
Level 2	Suggested	Data derived from a single randomized trials or large
		nonrandomized trial
Level 3	Unresolved	Consensus of opinion of experts or small studies,
		retrospective studies, or registries
Grade A	Strongly	Well-conducted randomized controlled trial (RCT) with 100 or more patients
	Recommended	including meta-analysis
Grade B	Recommended	Poorly controlled RCT, well-conducted case control
		or observational study
Grade C	Suggested	Expert opinion
CPP	Clinical Practice Points	Evidence not sought. A practice point has been made by the guideline development group where important issues arose from the discussion of evidence-based or clinical consensus recommendations

GENERAL PRINCIPLES OF BLOOD TRANSFUSION

Blood transfusion is a relatively common procedure in the practice of obstetrics and gynecology and is governed by certain general principles as follows.

Consent for Blood Products

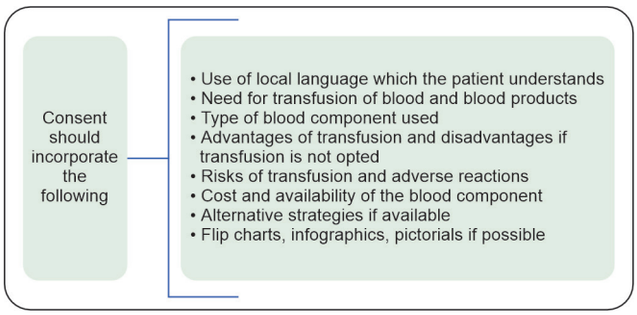
Practice Recommendations

Prior to administering a blood transfusion, valid consent should be obtained whenever possible.	Grade B
The consent must be legal and informed.	Grade B
Information on blood transfusion should be given retrospectively in an emergency situation, where obtaining consent is not practical.	CPP
In the patient's case notes, the justification for the transfusion and a record of the consent should be noted.	CPP
All components of the process for obtaining consent, must take into account current local, regional, state, national, and international laws and rules.	Grade B

There may be variations related to:

- Patients' capacity to provide a valid consent, e.g., the patient may be in shock and unable to provide consent
- Age of patient: major versus minor
- Type of blood product: blood component versus plasma derived
- Valid consent duration: single transfusion versus the whole episode of care
- Type of documentation: either in patient care sheet or separate transfusion form.

Discussion: Following a consultation exercise, the Advisory Committee on the Safety of Blood, Tissues, and Organs (SaBTO) recommended that, valid consent for blood transfusion should be obtained, whenever possible before administering a transfusion. This may not necessitate to express written consent; however, it necessitates that patients receive information on risks and benefits as well as alternatives available with clear documentation in the clinical case sheet.[4] Individuals who require a blood transfusion in an emergency situation might not be able to offer informed consent before the transfusion. Nonetheless, transfusion should not be postponed, and information should be shared after the event.



Blood Grouping and Cross-Matching

Practice Recommendations

All pregnant women should have their blood grouping and Rh typing done at antenatal registration (EL3)	CPP
The document of blood group and Rh typing should be available with patient during antenatal visits and when she reports in labor	
Blood grouping, cross-matching process should follow locally relevant guidelines	
While providing blood transfusion, cross-matching sample should be fresh; less than 24 hours old	
For women who are at a high risk of blood transfusion, e.g., placenta previa, accreta, and blood and blood products should be reserved in blood bank of the health care unit	
If the screen sample is showing clinically significant red cell antibodies, then blood negative for the relative antigen should be cross-matched before transfusion	Grade A

Discussion: The goal of maternal antibody screening is to identify clinically significant antibodies that could harm the fetus or newborn, as well as antibodies that could make it difficult to procure compatible blood components for the mother. The presence of red cell antibodies may cause isoimmunization; thus, the blood group and antibody status of pregnant woman, should be tested at booking and at 28 weeks of gestation (EL3).[5]

Further testing of maternal blood should be done, when red cell antibodies are found in the booking sample, to determine specific antibody with its level and to assess the likelihood of isoimmunization and the woman should be managed appropriately.[5]

In the event of an emergency, prior grouping makes transfusion easier. In many Indian healthcare settings, grouping is available. Blood grouping can be completed quickly and efficiently in the laboratory on glass slides with the right reagents in 2 or 3 minutes in the event of an unscheduled patient in an emergency by trained technical staff.

Decision to Transfuse

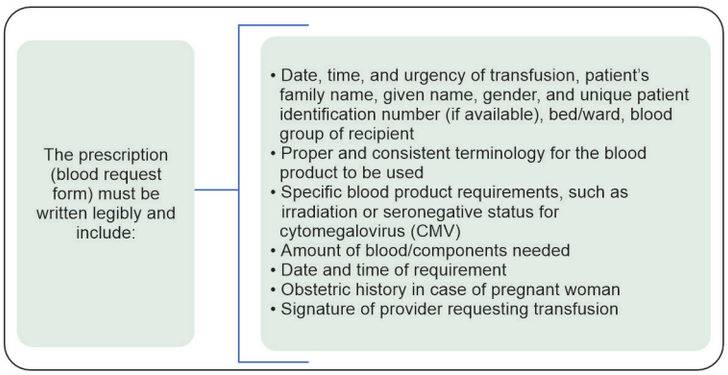
Practice Recommendations

Thorough clinical evaluation of the patient and her needs should dictate the decision to administer blood products	Grade B
The need for transfusion and other blood management techniques must be noted in the patients' case sheet	Grade B

Prescription for Blood Transfusion

Practice Recommendations

The prescription for blood and blood products should be provided prior to administering blood transfusion and should be clearly documented in the patients' case notes. It is a written authorization to administer the blood product	CPP
The need for transfusion should be evident and the provider is responsible to ensure it	Grade B
Ensure patient risk factors have been identified, assessed, and documented; for example, risk of transfusion-associated circulatory overload [TACO]	Grade C
Any known allergy to previous transfusion-associated reaction have to be been taken into consideration	Grade C
All prescriptions should follow local policy and regulations	CPP



Discussion: It is important that the pretransfusion sample collection must include the patient's identification details. Blood samples of recipient should be obtained: (i) in a stoppered plain vial/tube containing anticoagulant, (ii) with labels having: the patient's full name and identification number. The request must include the clinical indication for the transfusion and any special blood product requirements for the patient.

Which Type of Blood/Component to Transfuse

Practice Recommendations

Recipient should receive ABO type specific compatible blood or red blood cell components	Grade A
Rh(D) negative recipient should receive Rh(D) negative blood or red blood cell components	Grade A
In the absence of ABO type specific blood, group O packed red cells can be transfused	CPP
In case clinically significant red cell antibodies are present, then blood negative for the relevant antigen should be cross-matched and transfused	Grade A
Red cell and component transfusion should be human immunodeficiency virus (HIV), hepatitis B surface antigen, hepatitis C virus (HCV), Venereal Disease Research Laboratory (VDRL), malarial parasite negative	Grade A

Discussion: To avoid the risk of RhD alloimmunization, Rh-negative pregnant women (and women of childbearing age) must receive only RhD-negative blood (EL2+). There is no recommendation to provide Kell-negative blood for transfusion in women of childbearing age in the Government of India (GOI) guidelines. The tests which are universally recommendation in India are antibody testing, blood grouping, hemoglobin content, HIV I and II antibodies, hepatitis B surface antigen, hepatitis C antibodies, malarial parasites, syphillis, and VDRL, are some more tests that can be performed.[6]

In case of major obstetric hemorrhage, blood should be provided immediately, without any delay and the initial blood unit can be group O-negative units if needed, with subsequent transfusion of cross-matched antigen-negative units when available.[7]

Equipment and Devices

Practice Recommendations

The transfusion should be given with sterile, pyrogen-free and disposable transfusion set with filter	Grade A
The transfusion should be started immediately on receipt of blood	CPP

Transfusions of blood components are carried out using filtered intravenous tubing. The filters are also used to stop the administration of particulate debris; their typical pore sizes range from 170 to 260 microns.

Identification of Recipient and Donor Unit

Practice Recommendations (CPP)

Immediately before transfusion, the doctor/transfusionist should verify the identification of the patient, the blood unit, blood group, and cross-matching report and associated records.
All identifications attached to the container should remain attached at least until the transfusion is over.
The blood compatibility report should be attached in the patient's file. Transfusion should be prescribed and administered under medical direction.
The doctor/transfusionist should observe the patient for an appropriate time at the initial stage and during the transfusion to observe any evidence of adverse reaction.

In cases of rapid transfusion, massive transfusion, exchange transfusion in infants, and patients with cold agglutinins, blood should be warmed to body temperature using a blood warming device. Blood should not be warmed to more than 37°C.

HOW TO REDUCE BLOOD TRANSFUSION - OPTIMIZATION OF HEMOGLOBIN IN ANTENATAL PERIOD

Introduction

According to the World Health Organization (WHO), anemia in pregnancy is defined as a hemoglobin concentration of less than 11 g/dL in the first and third trimesters and 10.5 g/dL in the second trimester.[8] The optimization of hemoglobin level in pregnancy can helping in restricting blood transfusion.[9,10]

Optimization of Hemoglobin Levels in the Antenatal Period

Government of India recommends hemoglobin estimation at 14–16 weeks, 20–24 weeks, 26–30 weeks again at 30–34 weeks (at every antenatal visit)	Grade A
WHO recommends once a week of intermittent iron and folic acid supplementation (120 mg elemental iron and 2.8 mg folic acid) in nonanemic pregnant women and adolescents	Grade B
MoHFW recommends intermittent iron and folic acid supplementation (100 mg elemental iron and 0.5 mg folic acid) in all females of reproductive age (15–45 years)	CPP
In endemic regions, the WHO recommends intermittent preventive treatment (IPT) for malaria with at least 2 doses of sulphadoxine-pyrimethamine (SP)	Grade B

Discussion: A Cochrane systematic review suggests that both intermittent and daily iron supplementation have similar effects on maternal and infant outcomes in the context of iron deficiency anemia during pregnancy. However, intermittent supplementation may be associated with a fewer side effects.[11] Intermittent iron supplementation may be a feasible alternative to daily supplementation for pregnant women who are not anemic and have adequate antenatal care.

Correction: Oral and Parenteral Iron

Practice Recommendations for Iron Supplements

Oral iron should be the preferred first-line treatment for iron deficiency.[12]	Grade A
MoHFW, Government of India, recommends a single dose of 400 mg of albendazole tablet in the second trimester.	Grade A
100 mg of iron and 400 µg of folic acid daily, at least for 100 days starting after the first trimester, from 14–16 weeks of gestation, followed by the same for 6 months in the postpartum period is recommended by GOI [Ministry of Health and Family Welfare (MoHFW)].	CPP
In established mild-to-moderate anemia in pregnancy, daily supplementation of 120 mg of elemental iron and 400 µg of folic acid is recommended by the WHO.[13]	CPP
Intramuscular (IM) iron therapy in divided doses with oral folic acid in moderate anemia (MoHFW)	CPP
Standard prophylactic dose, after the Hb is normalized for the remaining term of pregnancy (WHO & MoHFW)	CPP
Parenteral iron is indicated when oral iron is not tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient time for oral supplementation to be effective (RCOG guidelines 2015).	CPP
Iron infusion should be carried out in a health facility with adequate supervision and availability for the management of anaphylaxis.	CPP
Sensitivity test prior to infusion is recommended.	CPP

Intramuscular dextran, intravenous (IV) iron sucrose, and ferric carboxymaltose (FCM) are the options studied in pregnant women. Iron dextran is associated with hypersensitivity (more frequent than IV iron). An Indian study in pregnant women showed that intravenous iron sucrose complex (200 mg twice weekly) produced a significant improvement in hemoglobin (Hb) raised from 7.63 ± 0.61 to 11.20 ± 0.73 g% ($p < 0.001$) after 8 weeks of therapy.[14] Ferric carboxymaltose - Assessment of Safety and efficacy in Pregnancy (FER-ASP trial) concluded that FCM is a better option than oral iron in effective and rapid management of anemia in pregnancy.[15] Another randomized trial FCM versus iron sucrose complex IV iron proposes that it is a noninferior option (Jose A et al., 2019).[16]

Practice Recommendations

Severe anemia during pregnancy (Hb <7 g/dL) warrants hospitalization and evaluation of cause irrespective of the period of gestation	Grade A
Valid consent should be obtained where possible prior to administering a blood transfusion	Grade A, Level 3
Packed red blood cell (RBC) transfusion is encouraged in pregnancy rather than whole blood transfusion	Grade A, Level 3
Single unit transfusion followed by reassessment if deemed necessary	Grade B, Level 3
Severe anemia (Hb below 7 gm/dL) in pregnancy warrants transfusion in any trimester	Grade C
No woman should have Hb level below 10 g/dL before going into labor	CPP
In a woman at a high risk of emergency transfusion, e.g. placenta previa, and with no clinically significant alloantibodies, group and screen samples should be sent once a week to exclude or identify any new antibody formation and to keep blood available if necessary (RCOG)[7]	Grade C

Indications of Blood Transfusion in Pregnancy (Fig. 1)

Practice Recommendations (Grade B)

- Antepartum
  - Pregnancy less than 34 weeks
    - Hb less than 5 gm/dL (with/without signs of heart failure)
    - Hb between 5–7 gm/dL (with signs of heart failure)
  - Pregnancy more than 34 weeks
    - Hb less than 7 gm/dL (without signs of heart failure)
    - Severe anemia with heart failure
  - Anemia due to acute hemorrhage
    - Hb at or below 6 gm/dL
    - Ongoing hemorrhage with hemodynamic instability (Hb estimation not needed)

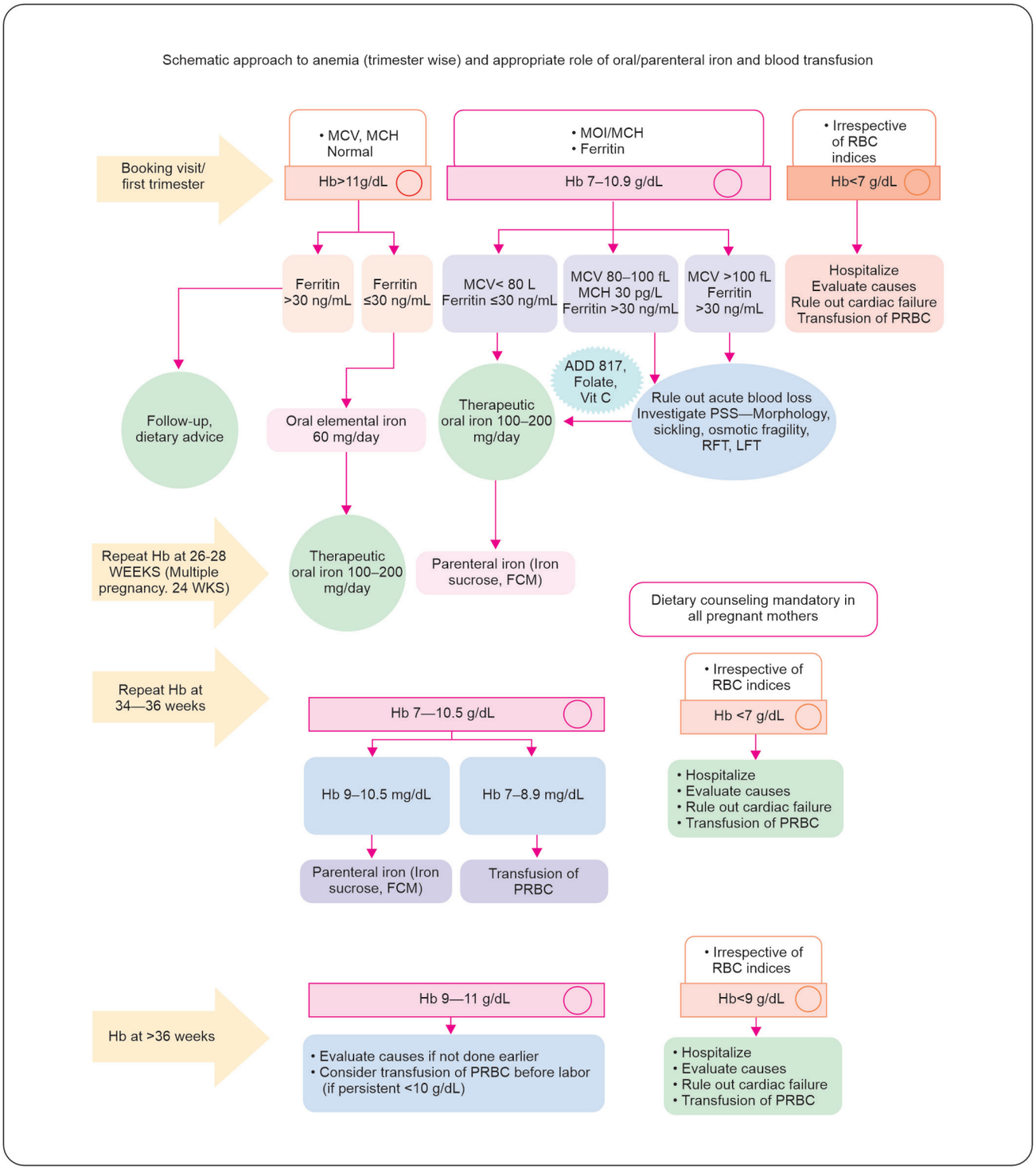


Fig. 1: Trimester-wise schematic approach to anemia and role of blood transfusion
Abbreviations: Hb: Hemoglobin; FCM: Ferric carboxymaltose; LFT: Liver function test; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; PRBC: Packed red blood cell; PSS: Physiological saline solution; RBC: Red blood cell; RFT: Renal function test

  - Nonnutritional deficiency anemia
    - Hemolytic anemia
    - Bone marrow deficiency
- Intrapartum
  - Hb less than 7 gm/dL
  - Clinical indication
- Postpartum
  - Hb less than 7 gm/dL
  - Ongoing hemorrhage with hemodynamic instability

Cell Salvage

Cell salvage was initially met with negativism, with concern about a possible threat of amniotic fluid embolism (due to amniotic fluid derived tissue factor). Over the years, scientific advances and evidences have changed the recommendations.

Practice Recommendations

Cell salvage is an option for patients where the anticipated blood loss is great enough to induce anemia or expected to exceed 20% of estimated blood volume	Grade C
Consent should be obtained for intraoperative cell salvage (IOCS) where possible and its use in obstetric patients should be done by a multidisciplinary team and subject to audit and monitoring	Grade C
In case of RhD-negative women (nonsensitized) undergoing IOCS during cesarean section where cord blood group is confirmed as RhD positive (or unknown), a minimum dose of 1,500 IU anti-D immunoglobulin should be administered following the reinfusion of salvaged red cells	Grade C

Discussion: Current evidence supports the use of intraoperative cell salvage (IOCS) in maternal health; however, high-quality randomized trials are needed to recommend routine use. Only multidisciplinary teams with regular IOCS experience should carry out this procedure, according to the National Institute for Health and Care Excellence (NICE) guideline on IOCS in obstetrics.

BLOOD COMPONENTS[17]

The availability of donated blood is always less than its requirement. This limited supply was the main driving force which led to the development of blood segregation techniques for the separation of whole blood in different components, each having important clinical usage. This facilitates the longer shelf-life, better usages of resources, and maximum use of available blood.

Whole Blood

In today's era, there are very little scope for whole blood transfusion. Various components should be separated from the whole blood and components should be replaced whenever required.

Packed Red Blood Cells (PRBC)

PRBC is prepared by the centrifugation of whole blood, achieving a hematocrit of 70–80%. Each bag raises Hb level by 0.5 g to 1 g/dL. The survival rate of blood cells decreases from 90% with immediate transfusion to 65% at 6 weeks of storage.

Practice Recommendations

PRBC tranfustion indication in Obstetrics: • Severe anemia (Hb <7 g/dL) due to any cause • Hemoglobinopathies • Obstetric hemorrhage	Level 3, Grade C

Irradiated - PRBC

The indications of irradiated PRBC transfusion:

- Allo/auto-HPC transplant recipients
- Intrauterine transfusion
- Highly immunosuppressed patients at risk for complication [graft-versus-host disease (GVHD)]
- Neonates/infants undergoing exchange transfusion or extracorporeal membrane oxygenation (ECMO)
- Cellular immune deficiency.

Platelets

Platelet transfusion recommendations:

Transfusion threshold & target	Grade D
Maintain the platelet concentration 50 x 10^3/dL in actively bleeding patient	Level 3
Ideally ABO compatible, if not available, any group platelet can be transfused	Level 3
Anti-D 300 IU should be given in RhD-negative women receiving RhD-positive platelet	Level 3
Transfusion trigger <75 x 10^3/dL in ongoing bleeding	Level 3
Target >50 x 10^3/dL for anesthesia and delivery	Level 3
Platelet transfusion, even without bleeding, if platelet counts <20 x 10^3/dL	Level 3

Discussion: It should be ABO and Rh compatible, since donor plasma is present. The evaluation of response to platelet transfusion is measured by corrected count increment (CCI):

CCI = [post transfusion count - pretransfusion count/number of platelets transfused × 10^{11}] × (Body surface area in square meters).[18] The platelet transfusion response is adequate if the CCI is 10 × 10^9/mL after one hour, and after 18–24 hours an increment of 7.5 × 10^9/mL is expected. Patients with less CCI are likely to have received multiple transfusions and have anti-HLA class 1 antibodies. These patients are best served by Single Donor Apheresis Platelet.

Practice Recommendations

Transfusion threshold & target: Grade D, Level 4

In case of massive hemorrhage, transfuse 12–15 mL/kg for every 6 unit of PRBC. Therapeutic goal should be prothrombin (PT)/activated partial thromboplastin time (APTT) <1.5 times control and international normalized ratio (INR) 1.5[19]	Level 4
Microvascular bleeding correction in massively transfused patients with >1 blood volume or when PT/INR/APTT cannot be measured timely. Reversal of warfarin therapy	Level 4
If PT/APTT not known, use a 1:1 ratio RBC:FFP after 4 units RBC have been transfused until results of hemostatic tests are known	Level 4

Discussion: Fresh frozen plasma (FFP) contains the components of coagulation, fibrinolytic, and complement systems, particularly factors V and VIII, which gradually decline during the storage of blood. ABO and Rh-specific plasma should be used. If not available, FFP of different group maybe used provided it does not possess high-titer of anti-A/anti-B antibody.

Cryoprecipitate: Cryoprecipitate contains factor VIII: C (i.e., procoagulant activity), factor VIII: vWF (i.e., von Willebrand factor), fibrinogen, factor XIII, and fibronectin.

Practice Recommendations

Cryoprecipitate transfusion is recommended in a standard dose of two 5-unit pools. Transfuse early in major obstetric hemorrhage. Further cryoprecipitate transfusion should be guided by fibrinogen results, aiming for levels >1.5 g/L.	Grade C, Level 4

Fibrinogen Concentrates

Practice Recommendations in Obstetric Hemorrhage

Cryoprecipitate may be transfused if fibrinogen <1 g/L. For "relentless" bleeding, up to 10 units (2 packs) of cryoprecipitate may be given empirically.	Grade C, Level 4

Discussion: Low levels of fibrinogen have been found to be associated with an increased risk of life-threatening hemorrhage.[20] A systematic review of 5 randomized trials and 15 nonrandomized studies concluded that "prothrombin complex and fibrinogen concentrations were not superior to conventional blood components for the treatment of perioperative coagulopathy in bleeding patients".[21] They can be considered early in patients receiving massive transfusion as diffuse intravascular coagulation (DIC) is often present. Cryoprecipitate is an adjunct in massively transfused patients when fibrinogen concentrations cannot be measured in a time.

BLOOD TRANSFUSION IN MAJOR OBSTETRIC HEMORRHAGE

Blood flow to the uterus is around 700 mL/minute at term and bleeding can be dramatic and rapidly fatal.[22] Major hemorrhage remains an important cause of maternal mortality in India, leading to 38% of maternal mortality.

Practice Recommendations

The cornerstones of resuscitation during postpartum hemorrhage (PPH) are the restoration of both blood volume and oxygen-carrying capacity. Volume replacement must be undertaken on the basis that blood loss is often underestimated.	Level 3, Grade C
Compatible blood to replace red cell loss should be transfused as soon as available. The clinical picture should be the main determinant of the need for blood transfusion and time should not be unnecessarily spent awaiting laboratory results.[23]	
Obstetricians should draw on the expertise of their colleagues in anesthesia, hematology, and transfusion medicine in determining the most appropriate combination of intravenous clear fluids, blood and blood products for continuing resuscitation.	
The main therapeutic goals of the management of massive blood loss is maintaining:[24] Hb greater than 8 gm/dL platelet count greater than 50,000/dL prothrombin time (PT) less than 1 .5 times normal activated partial thromboplastin time (AP TT) less than 1.5 times normal fibrinogen greater than 2 g/L.	

Fresh Frozen Plasma

Plasma provides a balanced source of all coagulant factors and volume expansion. In vitro data show it may have additional actions, including a protective effect on the endothelium.[25] A general weight-adjusted dose of fresh frozen plasma (FFP) of 15–20 mL/kg is recommended.[26]	Level 2, Grade A
If no hemostatic results are available and bleeding is continuing, then, after 4 units of RBCs, FFP should be infused at a dose of 12–15 mL/kg until hemostatic test results are known.	Level 3, Grade C
If no hemostatic tests are available, early FFP should be considered for conditions with a suspected coagulopathy, such as placental abruption or amniotic fluid embolism, or where the detection of PPH has been delayed.	Level 3, Grade C

Fibronogen Replacement

Hypofibrinogenemia is common in major hemorrhage, but there is very limited evidence to define the critical levels of fibrinogen on which to base decisions to administer fibrinogen, or the role of early empirical supplementation.	Level 2, Grade B
Fibrinogen supplementation should be given if fibrinogen concentrations fall below 1.5 g/L.	Level 2, Grade B
In patients with critical hypofibrinogenemia (<1 g/L). FFP contains insufficient fibrinogen to achieve the rapid rise in levels required to support hemostasis, and supplementation in the form of cryoprecipitate or fibrinogen concentrate should be offered.	Level 3, Grade C
Administer 2 pools of cryoprecipitate if hemorrhage is ongoing and fibrinogen less than 2 g/L.	Level 3, Grade C
Clinical data do not support one form of concentrated fibrinogen replacement over the other (i.e. cryoprecipitate or fibrinogen concentrate) and there is a paucity of cost-effectiveness comparative research between fibrinogen concentrate and cryoprecipitate.	Level 3, Grade C

Cryoprecipitate is the standard concentrated source of fibrinogen. Two 5-donor pools may increase fibrinogen in an adult by ~1 g/L, although recognizing the limitation of a nonweight-adjusted dose and that the (sustained) increase in fibrinogen in patients with bleeding may be less.[27]	CPP
Fibrinogen concentrate may also be considered as an alternative for the management of bleeding in patients: 4–5 g of fibrinogen concentrate may increase fibrinogen in an adult by ~1 g/L.	CPP

Platelets

Significant thrombocytopenia is considered a late event in major hemorrhage, typically seen after a loss of at least 1.5 blood volumes.[28]	Level 2, Grade A
As a pragmatic approach in cases of major bleeding, it is suggested that platelet transfusion should be given to maintain the platelet count at >50,000/dL, although higher thresholds may be indicated in actively bleeding patients with failing platelet counts.	CPP
Administer 1 pool of platelets if hemorrhage is ongoing and platelet count less than 75,000/dL.	Level 2, Grade A
Patients presenting with major bleeding may be on antiplatelet medications. Platelet transfusions are considered a safe and potentially effective intervention in major hemorrhage in these patients.	CPP

Selection of Red Cell Units for Transfusion

Major obstetric hemorrhage protocols must include the provision of emergency blood with an immediate issue of group O, Rhesus D (RhD)-negative units, with a switch to group-specific blood as soon as feasible.	Level 3, Grade C
Every stand-alone delivery unit should have an identified nearby blood bank and liaison with the same. The phone numbers of the blood bank should be displayed in prominent areas for easy accessibility.	CPP
Intraoperative cell salvage can be considered for emergency use in PPH associated with cesarean section and with vaginal delivery if facility is available.	Level 3, Grade C

Obstetric Hemorrhage Management (Fig. 2)

There are limited RCT data on optimal strategies for RBC transfusion in obstetric bleeding.	
There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be based on both clinical and hematological assessment.	Level 1, Grade B
Overall, a coagulopathy develops only in a minority of women with PPH, but is difficult to predict, and needs urgent identification and management to prevent bleeding becoming overwhelming.[29]	GPP
The cut-off thresholds for defining an abnormal PT/activated partial thromboplastin time (APTT) are typically based on non-pregnant individuals and do not take into consideration the rise in clotting factors seen during pregnancy and, therefore, a mildly elevated PT or APTT, should it develop, can represent a more significant hemostatic deficit during PPH.	Level 1, Grade B
If major bleeding is ongoing, and laboratory results are available, we suggest further FFP be administered aiming to maintain the PT ratio at <1.5 times mean normal (or equivalent).	Level 2, Grade C
Serial monitoring of coagulation tests is recommended, however, evidence on duration is lacking.	Level 2, Grade B
We suggest that serial hemostatic tests should be checked regularly, every 2 hours depending on the severity of the hemorrhage, to guide and ensure the appropriate use of hemostatic blood components.	Level 1, Grade B

MASSIVE TRANSFUSION PROTOCOL

Introduction

Massive transfusion is a life-saving intervention in the setting of hemorrhagic shock.[30] With a better understanding of the pathophysiology of hemorrhagic shock, resuscitation of patients with massive hemorrhage has advanced from reactive, supportive treatment with crystalloid, PRBC, and laboratory report-based use of coagulation factors to the use of proactive standardized protocols called massive transfusion protocols (MTPs). MTP describes managing blood transfusion requirements in major bleeding episodes and ensuring the judicious use of blood and blood components.

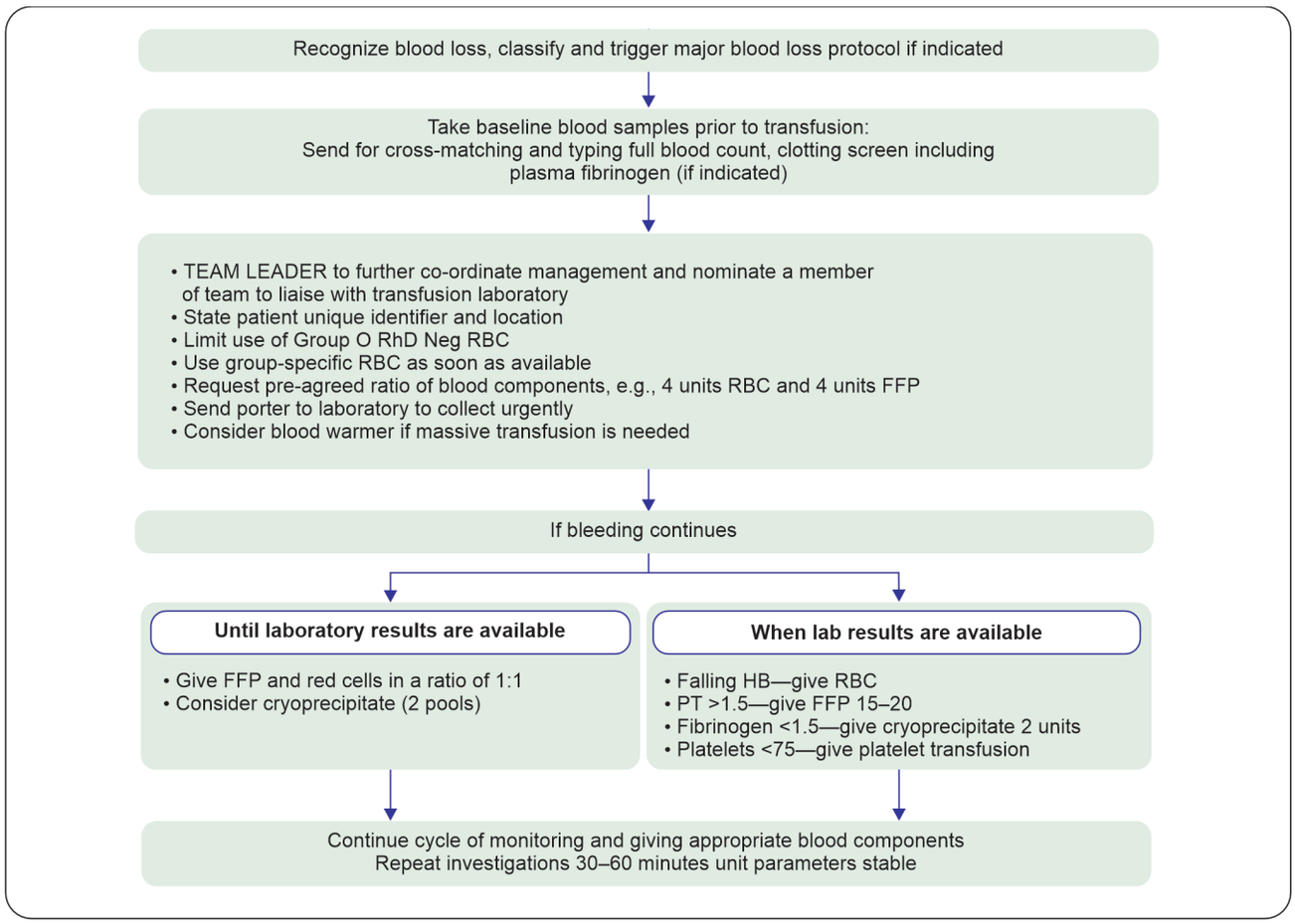


Fig. 2: Schematic management of obstetric hemorrhage
Abbreviations: FFP: Fresh frozen plasma; Hb: Hemoglobin; PT: Prothrombin time; RBC: Red blood cell

Various definitions of massive blood transfusion (MBT) have been published in the medical literature, such as:

- Replacement of one entire blood volume within 24 hours
- Transfusion of >10 units of packed red blood cells (PRBCs) in 24 hours
- Transfusion of >4 units of PRBCs in 1 hour when ongoing need is foreseeable
- 50% of total blood volume (TBV) is replaced within 3 hours.

Rationale

Mild-to-moderate blood loss can be managed with crystalloid or colloid infusions alone. With increasing loss, dilutional anemia coagulopathy sets in, leading to refractory hemorrhage. MTPs are designed to interrupt the lethal triad of acidosis, hypothermia, and coagulopathy that develops with massive transfusion. This improves outcomes by the concurrent supplementation of PRBCs, plasma and platelets in fixed ratios, aiming to maintain the physiological constitution of blood, and preventing the deficits of one or more constituents.[31]

Indication for MTP Protocol

A clinician activates massive transfusion protocols in response to an expected massive blood transfusion.

Criteria to trigger the activation of an MTP should be based on clinical judgement and can be aided by the following score (Grade A):

Score	*Parameters*
American College of Surgeons Advanced Trauma Life Support (ATLS) classification of blood loss[32]	Approximate blood loss, heart rate, blood pressure, pulse pressure, respiratory rate, urine output, Glasgow coma scale score, base deficit

Practice Recommendations

Massive transfusion protocol is a life-saving measure. However, several studies are needed to establish the safety and efficacy of MTP in obstetric patients.	Level 2, Grade A
1:1 :1 continues to remain the most widely used metric to guide MTPs worldwide. (RBC: FFP: Platelet)	Level 2, Grade B

Discussion: The rationale for the 1:1:1 ratio is that it more closely resembles whole blood. A review of patients at a US combat hospital demonstrated reduced mortality from 66% to 19% when the RBC: plasma ratio decreased from 8:1 to 2:1.38. In clinical practice, 1:1:1 continues to remain the most widely used metric to guide MTPs worldwide.[28]

The Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study demonstrated improved in-hospital mortality with RBC: plasma and RBC: platelet ratios 2:1 in the first 6 hours. The follow-up Pragmatic Randomised Optimal Platelet and Plasma Ratios (PROPPR) trial is a randomized trial to evaluate ratios; either a 1:1:1 (higher ratio) or a 2:1:1 (lower ratio) with the primary outcome of survival and complications.[32]

MTP in Obstetric Settings

Practice Recommendations

Maternity services should develop a massive transfusion protocol and activate them early	CPP
FIGO (International Federation of Gynecology and Obstetrics) recommends the 1:1:1 ratio, with typical rounds comprising 6 units PRBC, 6 units FFP, 6 units PLT or 1 platelet apheresis, and 10 units of cryoprecipitate.	Grade B

Discussion: The use of MTP in the obstetric setting shows a significant variation across countries. The incidence of massive transfusion was approximately 21 women per 100,000 maternities for the UK, Australia, and Italy. In Denmark, Netherlands, and France, the incidence was 82, 66, and 69 per 100,000, respectively. Specific guidelines advise that maternity services develop an MTP and activate them early.[33]

Ideal Ratio

The International Federation of Gynecology and Obstetrics (FIGO) recommends the 1 :1 :1 ratio, with typical rounds comprising 6 units PRBC, 6 units FFP, 6 units PLT or 1 platelet apheresis, and 10 units of cryoprecipitate.[34] The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend a 6:4:1 ratio - 6 units PRBCs, 4 units FFP, 1 apheresis pack of platelets.[35] The utilized dose of recombinant factor VII is based on local expert opinion **(Table 1)**. Several studies also show an association between fibrinogen levels and PPH, signifying a future role of fibrinogen supplementation in preventing and treating PPH.[36]

Table 1 Massive transfusion protocol - Pacheco LD et al.[37]

	PRBC	*FFP*	*Platelets*	*Cryoprecipitate*
Round 1	6 U	6 U	6 U	10 U
Round 2	6 U	6 U		20 U
Round 3	Recombinant activated factor VIIa (40 microgram/kg)			
Round 4	6 U	6 U	6U	10 U
Round 5	6 U	6 U		10 U
Round 6	Recombinant activated factor VII (40 microgram/kg)			

PATIENTS REFUSING BLOOD TRANSFUSION[38]

In case of hemorrhage, women who refuse blood products require faster care Grade B transitions from observation and fluid replacement to mechanical hemostasis (such as an intrauterine compression balloon) and hysterectomy than patients who can receive blood transfusions.

Patient blood management techniques, targeted treatment of anemia with parenteral iron, treating coagulopathy and hemoglobin-based oxygen carriers (HBOCs) can be the alternative options in such cases. Since blood replacement is not an option, achieving hemostasis as quickly and effectively as possible is essential.

Practice Recommendations

If there is significant ongoing bleeding, consider involving the second consultant and multidisciplinary care for managing the patient	Grade B
Identify hemorrhage risk factors	Grade B
In the absence of coagulopathy or in case hemodynamic parameters are yet to be corrected, do not postpone definitive surgical intervention	Grade A
Consider prophylactic tranexamic acid (1 g/10 min) as a preventative measure just before delivery	Grade B
Transfer to facility providing more intensive care	CPP

TRANSFUSION REACTIONS AND THEIR MANAGEMENT (Annexure 1)

Background

Transfusion reactions (TR) occur when a patient who receives a transfusion of blood or blood products that their body has ultimately rejected. Studies - in nonpregnant patients - have shown that up to 20% of transfusions may result in some form of complications. Pregnancy poses a special challenge as the immune response in pregnancy is different from that in the nonpregnant state. The nature or onset of complications may be affected as pregnancy is known to cause the formation of red cells alloantibodies. Pregnancy is associated with the higher levels of leukocyte antibodies and has a modulating effect on the immune system.[39]

Types of Reactions (Tables 2 and 3)

These can be broadly classified into two: immune-based and nonimmune-based. The spectrum of symptoms ranges from mild, such as febrile or urticarial reactions, to severe. In some cases, reactions can be life-threatening. Deaths linked to transfusion reactions have been reported at a rate of 1 per every 100,000 transfused units.[40]

Practice Recommendations

Review the blood unit and compare with the accompanying form, the serial numbers, blood group, Rh typing, dates of collection and expiry, and other identifying characteristics mentioned.	Grade A
The most frequent reactions are fever, chills, pruritus, or urticarial rashes, which typically resolve promptly without specific treatment or complications. Symptomatic relief and clinical observation should suffice in this group of patients.	GPP
Hemolytic transfusion reactions which occur during or within 24 hours after the administration of a blood product are usually owing to the transfusion of incompatible red blood cells (RBCs) or more rarely owing to a large volume of incompatible plasma. In such cases, the transfusion needs to be stopped immediately, injectable paracetamol, antihistamines, epinephrine, diuretics, steroids, and oxygen will be required depending on the severity of the reaction.	Grade A
The Transfusion Reaction Reporting Form needs to be filled, blood and urine samples should be collected and the original blood bag should be submitted back to the blood bank for further investigation.	Grade A
Multidisciplinary care with a transfer to intensive care unit (ICU) may be essential in cases of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) with dyspnea, pulmonary edema, and hypotension.	Grade A
Report the adverse event to the Blood Bank Officer in appropriate form.	CPP

Table 2 Summary of acute noninfectious transfusion reactions with management

Acute reaction	*Key features*	*Treatment*
Acute hemolytic transfusion reaction	Acute kidney injury, anemia, chills, disseminated intravascular coagulation, dyspnea, fever, hematuria, hemolysis, pain, rigors, shock, death	Supportive care; transfusion of compatible blood products; maintenance of urine output
Allergic and anaphylactic or anaphylactoid transfusion reaction	Dyspnea, hypotension, localized angioedema, pruritus, shock, urticaria, wheezing	Supportive care; antihistamines; bronchodilators; glucocorticoids; epinephrine; consideration of washed or volume-reduced blood products for severe and refractory cases
Febrile nonhemolytic transfusion reaction	Chills, hypertension, rigors, tachycardia, tachypnea, temperature increase 1°C (1.8°F)	Supportive care; antipyretics; meperidine (Demerol); transfusion of leuko-reduced blood products: consideration of washed or volume-reduced blood products for severe and refractory cases
Transfusion-associated	Bilateral pulmonary interstitial infiltrates, chills, dyspnea, fever, hypertension, hypoxemia, circulatory overload jugular venous distention, peripheral edema, pleural effusions, tachycardia, tachypnea	Supportive care; diuresis; dialysis; placement of patient into sitting position
Transfusion-related acute lung injury	Bilateral pulmonary interstitial infiltrates, blood pressure changes, chills, dyspnea, fever, hypoxemia, tachycardia, tachypnea	Supportive care

Table 3 Summary of delayed noninfectious transfusion reactions of transfusion[41]

Delayed reaction	*Key features*	*Management*
Alloimmunization	Difficulty obtaining compatible cellular blood products, hemolysis, occurs when antigen-negative patients are transfused with antigen-positive blood products, platelet refractoriness, production of antibodies against foreign antigens	Restrictive transfusion strategy; transfusion of compatible blood products
Delayed hemolytic transfusion reaction	Anemia, chills, dark urine, dyspnea, fever, jaundice, pain, rigors	Supportive care; transfusion of compatible blood products
Post-transfusion purpura[42]	Rigors, bleeding, death, petechiae, purpura, rapid-onset thrombocytopenia	Supportive care; intravenous immunoglobulin; glucocorticoids; therapeutic plasma exchange
Transfusion-associated graft versus-host disease	Abdominal pain, death, diarrhea, erythema, fever, hepatic dysfunction, maculopapular rash, nausea, pancytopenia, vomiting	Supportive care
Iron overload	Cardiomyopathy, endocrine organ dysfunction, hepatic injury	Restrictive transfusion strategy; iron chelation therapy

Hemolytic Reactions

The risk of hemolytic transfusion reactions is approximately 1 in 70,000. When they occur during or within 24 hours after the administration of a blood product, this is usually owing to the transfusion of incompatible red blood cells (RBCs) or more rarely owing to a large volume of incompatible plasma.

These are broadly classified into:

- Immediate intravascular hemolytic transfusion reactions (mostly due to ABO incompatibility).
- Delayed hemolytic transfusion reactions (predominantly extravascular; antibodies to Jk and Rh are the usual causes).
- Pseudohemolytic transfusion reactions are similar to hemolytic reactions, but no incompatibility is detected (drugs and bacterial contamination are the usual causes).

Prevention

One critical consideration regarding transfusion reactions is accurate blood typing. If a person receives blood that is not compatible with their blood type, their immune system launches an attack on the transfused blood, resulting in a transfusion reaction. Hence, accurate blood typing and cross-matching to ensure compatibility is of a paramount importance	Grade A

Another important factor in preventing transfusion reactions is proper storage and handling of blood products. Blood products must be stored at the correct temperature and must be used by expiration dates, as they can become less effective or even harmful if not stored properly. In addition, all blood donations go through a rigorous screening process to minimize the risk of transmitting infections to patients who receive transfusions.

Transfusion reaction should be reported in Transfusion Reaction Reporting Form. It is a simple one-page form divided into six sections as follows **(Annexure 2)**:

- Patient information
- Transfusion product(s) details
- Nature of adverse reaction(s)
- Outcome of adverse reaction(s)
- Reporter
- Causality assessment.

RECENT ADVANCES IN BLOOD TRANSFUSION THERAPY

Restrictive Blood Transfusion Strategies

Clinical Practice Guidelines from the American Association of Blood Banking (AABB) have recommended to restrict blood transfusion to patients with an Hb <7 gm/dL.	Grade A
With an Hb of 7–10 gm/dL, restrictive blood transfusions are recommended based on the expected blood loss, compensatory ability, and metabolic rate.[43]	Grade A

Discussion: The advantages of this approach are that blood storage is saved, there is a reduction in transfusion-related adverse events, infections, immunological risks, and lower incidence of circulatory overload.

Pathogen-reduced Blood Products

We now have methods to reduce the risk of the transmission of pathogens via blood transfusion. Pathogen reduction technology (PRT) is a method of treating blood products to reduce the risk of transfusion-transmitted infections (TTIs). This works using a combination of light and chemicals to inactivate pathogens that may be present in blood products. PRT has been shown to be effective in reducing the risk of the transmission of pathogens including viruses such as HIV, hepatitis B and C, and bacteria such as *Yersinia enterocolitica and Staphylococcus aureus.*[44] PRT can be used to treat a variety of blood products including packed red blood cells, platelets, and plasma.

Blood Substitutes

These include plasma and volume expanders, which can be used in certain conditions and scenarios. Such blood substitutes are broadly categorized into two classes: hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbon (PFC)-based products. HBOCs include recombinant hemoglobin where there is cross-linking, polymerization, and encapsulation to create alternative molecules. PFC-based products have been withdrawn in 1994 owing to the complexity of their use **(Table 4)**.[45]

Table 4 Summary of perfluorocarbons

Oxyglobin	HBOC	Trials completed by late 1990s, Canine anemia	Approved: Veterinary Medicine
Hemopure	HBOC	Completed (South Africa)	Approved (South Africa), may be withdrawn
PolyHeme	HBOC	Phase III Trial (U.S): Raised oxygen levels without serious side effects	No approval, further research needed
MP40X	HBOC	Phase II Trials (U.S): raised oxygen levels without serious side effects	No approval, further research needed
Hemotech	HBOC	Phase I Trials : No toxicity	No approval, further research needed
Engineered Hemoglobin	HBOC	Preliminary studies: Minimal side effects, good oxygen delivery	No approval, further research needed

Abbreviation: HBOC: Hemoglobin-based oxygen carrier

Recombinant Factor VIIa

Recombinant factor VIIa is an approved medication for treating inherited bleeding problems is (rFVIIa). However, its role in PPH is still under evaluation.

Practice Recommendations

Recombinant factor VIIa if used: hematologist consultation should be taken along with ensuring correction of hypofibrinogenemia, thrombocytopenia, and acidosis.	Level 4, Grade C

Recombinant Factor VIII and IX

Factor IX is an important protein in the coagulation cascade. Factor IXa cleaves and activates X to Xa which activates thrombin to form a blood clot. Recombinant FIXa (rFIXa) is produced using genetic engineering techniques and is designed to mimic the naturally occurring activated Factor IX. The rFIXa has a longer half-life than traditional factor IX concentrates. It may be a lifesaving drug in patients with PPH and hepatic disorders.

Application of Artificial Intelligence

The use of artificial intelligence (AI) and machine learning models in blood donation and transfusion is now being utilized increasingly. AI is being used to analyze the vast amounts of data to optimize blood donation and transfusion practices. For example, AI can be used to predict blood demand and ensure that the right blood products are available in the right quantities at the right time, though it will be some time before this can be widely available and applicable in mainstream clinical practice.

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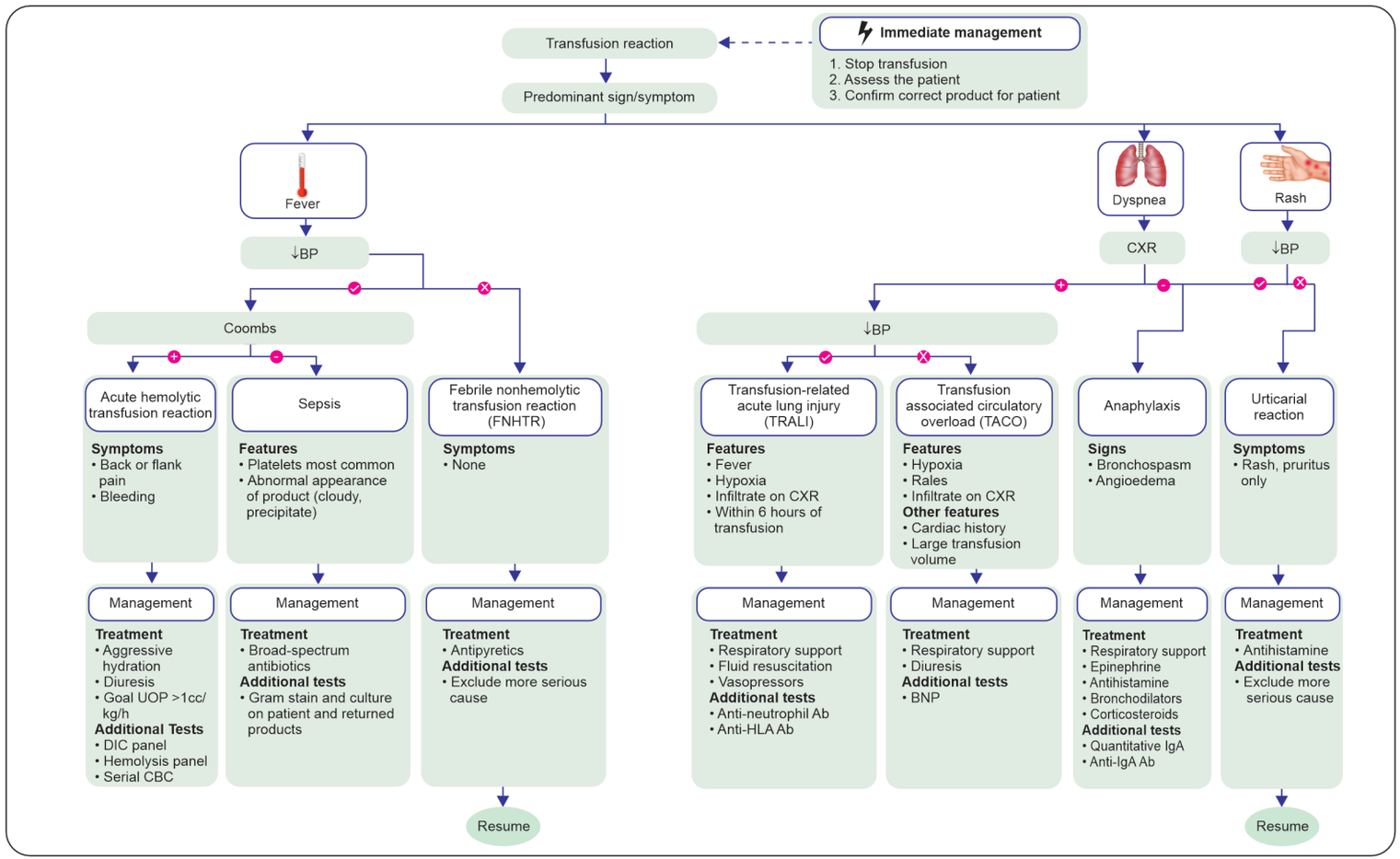
ANNEXURES

ANNEXURE 1: ALGORITHM FOR MANAGEMENT OF TRANSFUSION REACTIONS



Abbreviations: Ab: Antibody; BNP: B-type natriuretic peptide; BP: Blood pressure; CBC: Complete blood count; CXR: Chest X-ray; DIC: Disseminated intravascular coagulation; HLA: Human leukocyte antigen; Ig: Immunoglobulin; UOP: Urine output

ANNEXURE 2: STANDARDIZED TRANSFUSION REACTION REPORTING FORM (TRRF)

Transfusion Reaction Reporting Form (TRRF) for Blood & Blood Products

Indian Pharmacopoeia Commission-National Institute of Biologicals
Ministry of Health & Family Welfare-Govt. of India
HEMOVIGILANCE
(Pharmacovigilance Programme of India)

TRANSFUSION REACTIONS REPORTING FORM FOR BLOOD & BLOOD PRODUCTS

For reporting of Transfusion Reactions by Heathcare Professionals *Mandatory Field

A) PATIENT INFORMATION

Patient initials*.....DOB/Age in years*:.....Blood Group*..... Diagnosis.....Hospital Code No.....
Hospital Admission No*.....Sex* F ☐ M ☐
Date & Time of Transfusion*.....Date & Time of reaction*.....Date & Time of recovery.....

B) TRANSFUSION PRODUCT DETAILS*

Components	Select components	Unit number (transfused)	Expiry date	Manufacturer	Batch number	Indications	1st time/repeat transfusion (No. of repeats)
Whole Blood							
Red Blood Cells							
Platelets Apheresis							
Platelets Pooled RDP							
Solvent Detergent (SD) Plasma							
FFP							
Cryoprecipitate							
Any other	Manufacturer		Batch number		Expiry date		
Blood products (Please specify)							

C) NATURE OF ADVERSE REACTIONS*

	Reactions	Please Tick [✓]
1	Immunological Hemolysis due to ABO Incompatibility	
2	Immunological Hemolysis due to other Alloantibodies	
3	Non-Immunological Hemolysis	
4	Transfusion Transmitted Bacterial Infection	
5	Anaphylaxis/Hypersensitivity	
6	Transfusion Related Acute Lung Injury (**TRALI**)	
7	Transfusion Transmitted Viral Infection (**HBV**)	
8	Transfusion Transmitted Viral Infection (**HCV**)	
9	Transfusion Transmitted Viral Infection (**HIV-1/2**)	
10	Transfusion Transmitted Viral Infection, other (**Specify**)	
11	Transfusion Transmitted Parasitic Infection (**Malaria**)	
12	Transfusion Transmitted Parasitic Infection, other (**Specify**)	
13	Post Transfusion Purpura	
14	Transfusion Associated Graft versus Host Disease (**TAGvHD**)	
15	Febrile Non-Hemolytic Reactions (FNHTR)	
16	Transfusion Associated Dyspnea (TAD)	
17	Transfusion Associated Circulatory Overload (TACO)	
18	Other Reaction(s)	

D) OUTCOMES OF THE ADVERSE REACTIONS*

Death following the adverse reactions ☐
• Recovered ☐
• Recovered with sequelae ☐
• Permanently disabled ☐
• Unknown ☐

E) REPORTER*

Name and professional address:.....
.....
Pin Code:.....Email:.....
Tel No. (with STD code).....

Any other information.....

F) CAUSALITY ASSESSMENT*

Date of this report (DD/MM/YYYY)

Disclaimer - These recommendations for “BLOOD TRANSFUSION IN OBSTETRICS AND GYNECOLOGY” have been developed, to be of assistance to obstetricians, gynecologists, consulting physicians and general practitioners by providing guidance and recommendations for managing women with anemia and suffering from hemorrhagic conditions. The recommendations included here shouldn't be viewed as being exclusive of other concepts or as covering all legitimate strategies. The suggestions made here are not meant to dictate how a particular patient should be treated because they neither set a standard of care nor do they guarantee a particular result. To diagnose patients, choose dosages, and provide the best care possible while also taking the necessary safety precautions, clinicians must rely on their own experience and knowledge. The writers or contributors disclaim all responsibility for any harm and/or damage to people or property resulting from the use or operation of any techniques, goods, guidelines, or ideas presented in this content.