

# Blood Product Administration in Children and Young Adults Likely to Need a Solid Organ Transplant

October 2020

## TARGET POPULATION FOR THE RECOMMENDATION

### Inclusion Criteria

Children and young adults who are likely to require solid organ transplantation:

For heart transplant, patients with:

- single ventricle physiology
- cardiac dysfunction
- hypertrophic cardiomyopathy
- restrictive heart disease

For kidney transplant, patients with:

- Chronic Kidney Disease (CKD) stage 3 or higher (estimated GFR of < 60 ml/min/1.73 m<sup>2</sup>)
- on dialysis
- under evaluation or waitlisted for kidney transplantation
- have received a kidney transplant

For liver transplant, patients with:

- listed for liver transplantation
- having received a liver transplant

For lung transplant, patients with:

- listed for transplantation
- having received a lung transplant

For small bowel transplant, patients with:

- listed for transplantation
- having received a small bowel transplant

### Exclusion Criteria

Bone marrow transplant or hematopoietic stem cell transplant recipients

## EVIDENCE-BASED CARE RECOMMENDATIONS

### Clinical Assessment

#### Care Recommendation Statement 1

It is strongly recommended that the theoretical future risk of allosensitization should not prevent or delay administration of blood products in patients with life threatening conditions that could be reversed by blood product administration (*Local Consensus, 2020 [5]*).

Recommendation Strength  
**Strong**

#### Care Recommendation Statement 2

It is strongly recommended that the decision to administer blood products consider all perceived risks and benefits in each individual patient (*Scornik, 2013 [1a]*).

Recommendation Strength  
**Strong**

- **Note 1:** This includes the risk of allosensitization, which has been associated with longer wait times and increased risk of rejection and mortality in patients who are in need of kidney or heart transplantation (*Scornik, 2013 [1a]; McKee, 2018 [3a]; Ibrahim, 2011 [4a]*).

- **Note 2:** While there is little published evidence on how pre-transplant allosensitization impacts the outcomes of lung and small bowel transplant recipients, it is likely that allosensitization is associated with longer wait times and increased risk of rejection and mortality in those patients. (*Bond, 2000 [3a]; Gondolesi, 2006 [5b]*).
- **Note 3:** Studies suggest that pre-transplant allosensitization does not impact primary liver transplant wait times, but the impact of allosensitization on liver allograft outcomes (survival and rejection) is unclear (*Del Bello, 2017 [4a]*).

### Care Recommendation Statement 3

It is strongly recommended that transfusions for non-life-threatening events be done only after consultation with an appropriate solid organ transplant physician with the expectation that:

Recommendation Strength  
**Strong**

- both parties (primary team and the solid organ transplant team) understand the risks versus benefits of a blood product administration (*Local Consensus, 2020 [5]*)
- the appropriate preparation of the blood product will be specified by the transplant physician (*Local Consensus, 2020 [5]*).
- the “primary admitting service of record” will make the final decision of whether to administer or not administer the blood product (*Local Consensus [5]*)
- decision on modality for optimization (pharmacologic versus blood transfusion) should be done in consultation with all stakeholders (admitting service, medical transplant service and if applicable surgical service, and anesthesia)

(*Scornik, 2013 [1a]; Nelson, 2019 [2b]; McKee, 2018 [3a]; Dzik, 2002 [3a]; Magee, 2012 [3b]; Akgul, 2017 [4a]; Del Bello, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Pirim, 2015 [4a]; Sanz, 2010 [4a]*).

### Care Recommendation Statement 4

It is strongly recommended that all surgical decision-making regarding blood transfusion, including the patient’s transfusion threshold take place in the operating room between the attending surgeon and anesthesiologist prior to each case or procedure and shared with the team (*Local Consensus, 2020 [5]*).

Recommendation Strength  
**Strong**

- **Note 1:** For patients presenting for high risk procedures, blood products should be ordered prior to entering the operating room and available in the Haemobank prior to surgical incision (*Local Consensus, 2020 [5]*). (See appendix A for list of high-risk procedures)
- **Note 2:** For patients presenting for intermediate or low risk procedures, discussion amongst surgery, medical transplant and anesthesia should occur regarding need for blood product preparation (*Local Consensus, 2020 [5]*). (See appendix A for list of intermediate and low risk procedures)
- **Note 3:** Any procedure with an anticipated blood loss of  $\geq 7$  ml/kg should have a specific blood loss plan in place (*World Health Organization, 2009 [5b]*).
- **Note 4:** A patient's risk overall for intraoperative bleeding is not purely based on planned procedure but is determined by the surgeon in coordination with the anesthesiologist and other members of the operative team. This should be a thoughtful synthesis of multiple factors including, but not limited to:
  - the patient's size (and blood volume)
  - clinical condition
  - starting hemoglobin level
  - comorbidities that inhibit clotting (renal failure, hepatic synthetic dysfunction, innate clotting disorder)
  - medications that affect clotting and platelet function.

The frequency with which a particular procedure results in significant ( $\geq 7$  ml/kg) blood loss must be factored in, as well as the severity of bleeding for those times when it does occur. If a particular surgery rarely causes intraoperative bleeding, but the few times that it does may be of significant magnitude, or significant technical challenge to control (as in a subclavian vessel perforation or vena cava injury), such factors must be considered in estimating the patient's overall intraoperative bleeding risk (*Local Consensus, 2020 [5]*).

## Transfusion Thresholds

### Care Recommendation Statement 5

It is strongly recommended that a restrictive transfusion threshold (Hgb  $\leq$  7 g/dL) be utilized for patients without other medical conditions that would dictate higher thresholds (Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]).

Recommendation Strength  
**Strong**

- **Note 1:** Restrictive transfusion thresholds (Hgb  $\leq$  7 g/dL) result in fewer transfusions and are noninferior (regarding mortality) to liberal transfusion thresholds (Hgb  $\geq$  10 g/dL) (Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]).
- **Note 2:** Restrictive transfusion triggers (Hgb 7-8 g/dL) can be used for most patients (children and adults) (Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]).
- **Note 3:** Additional studies are needed to establish the blood count at which a blood transfusion is needed in patients who have suffered a heart attack or brain injury (Carson, 2016 [1a]).

### Care Recommendation Statement 6

It is strongly recommended that an intermediate hemoglobin concentration may justify a red blood cell transfusion based on:

Recommendation Strength  
**Strong**

- ongoing indication of organ ischemia
- potential or actual ongoing bleeding (rate and magnitude)
- patient's intravascular volume status
- patient's risk factors for complications of inadequate oxygenation
- low cardiopulmonary reserve and high oxygen consumption
- discussion with managing service

(Carson, 2016 [1a]).

## Leukoreduction & Indications

### Care Recommendation Statement 7

It is recommended that all patients receive leukoreduced units (Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).

Recommendation Strength  
**Moderate**

- **Note 1:** All red blood cells and platelets at Cincinnati Children's are leukoreduced (Local Consensus, 2020 [5]).
- **Note 2:** Each unit of whole blood or unmodified red cells contains roughly 2 to 5 x 10<sup>9</sup> leukocytes. The most effective current leukocyte reduction filters ("third generation") can achieve a three- to four-log (99.9 to 99.99%) reduction, leaving residual leukocyte counts below 5 x 10<sup>6</sup>, and generally below 1 x 10<sup>6</sup> (Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).
- **Note 3:** Leukoreduction may help to decrease the following:
  - febrile nonhemolytic transfusion reactions
  - human leukocyte antigen (HLA) alloimmunization (Nelson, 2019 [2b])
  - postoperative infection, bacterial contamination
  - cardiac reperfusion injury
 (Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).

## Irradiation and Indications

### Care Recommendation Statement 8

It is recommended that Gamma or X-irradiation of cellular blood components (red cell, platelet and granulocyte concentrates) be utilized to prevent transfusion-associated graft-versus-host disease (TA-GvHD) (a rare but almost invariably fatal complication of transfusion) (*Local Consensus, 2020 [5]*). However, irradiation of blood products should not delay blood product administration for life-threatening emergencies and will be waived in a massive transfusion scenario (*Local Consensus, 2020 [5]*).

Recommendation Strength  
**Moderate**

- Utilize Gamma or X-irradiation of cellular blood components (red cell, platelets, and granulocyte concentrates) to prevent TA-GvHD in the following:
  - blood products for intrauterine transfusion or neonatal exchange transfusion (*Treleaven, 2011 [5a]*)
  - blood products from first- or second-degree relatives and all HLA-selected components even if that patient is immunocompetent
  - for at least one year in the following situations:
    - severe T-lymphocyte immunodeficiency syndromes (*Treleaven, 2011 [5a]*)
      - **Note:** A clinical immunologist should be consulted for advice in cases where there is uncertainty (*Local Consensus, 2020 [5]*).
    - patients undergoing allogeneic or autologous HSCT, starting at the time of initiation of conditioning chemotherapy (*Treleaven, 2011 [5a]*)
    - patients with Hodgkin's lymphoma (*Treleaven, 2011 [5a]*)
    - patients treated with purine analogue drugs (*Treleaven, 2011 [5a]*)
    - patients who have been treated with alemtuzumab (anti-CD52) or anti-thymocyte globulin (ATG) (*Local Consensus, 2020 [5]*)
    - patients awaiting SOT with the peri-operative plan to use these T cell depleting agents (ATG/Campath) for induction of immunosuppression (*Local Consensus, 2020 [5]*)
  - indications may be extended more broadly in order to ensure coverage for all potential at-risk patients (*Local Consensus, 2020 [5]*).
    - **Note:** Examples at CCHMC include:
      - All patients < 4 months of age, to protect patients with undiagnosed congenital immune deficiencies as well as patients receiving neonatal exchange transfusions (*Local Consensus, 2020 [5]*).
      - All patients receiving malignancy/cancer-related treatments (chemotherapy/radiation), to protect these patients against TA-GvHD risk (*Local Consensus, 2020 [5]*).
- **Note:** It is not necessary to irradiate fresh frozen plasma (FFP), cryoprecipitate, or fractionated plasma products (*Treleaven, 2011 [5a]*).

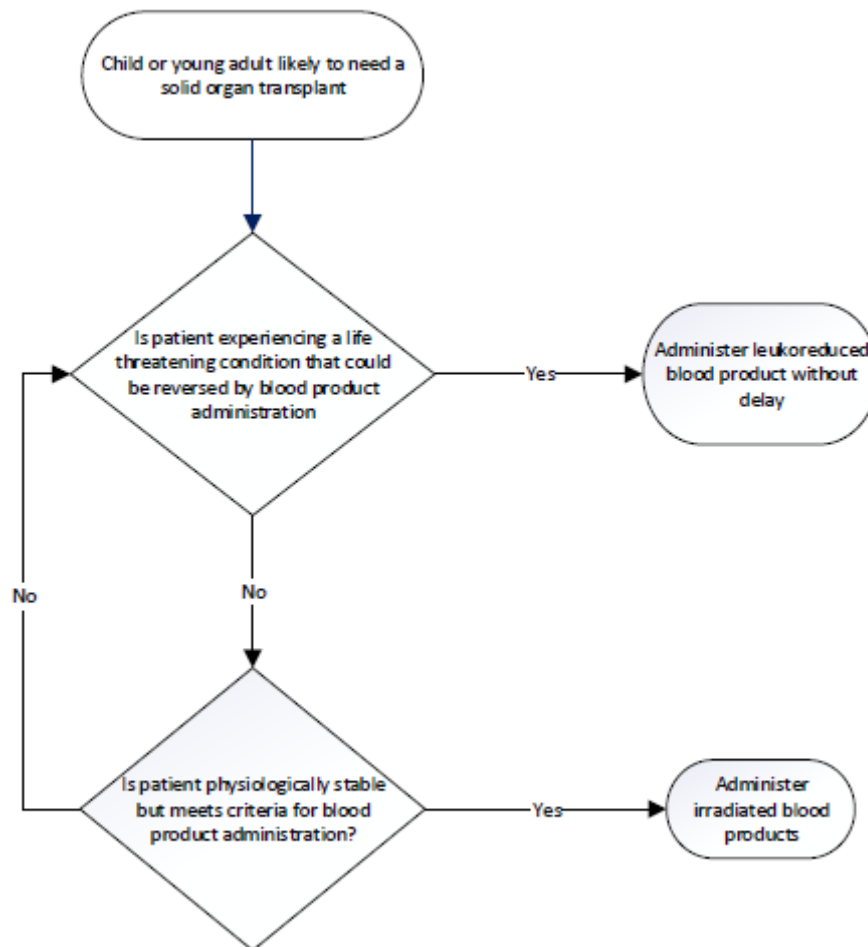
### Care Recommendation Statement 9

It is recommended that children and young adults who have had solid organ transplantation or who are likely to require solid organ transplantation receive irradiated blood products (*Local Consensus, 2020 [5]*).

Recommendation Strength  
**Moderate**

- **Note 1:** Preliminary data is not conclusive but suggests that irradiation of blood products may help to reduce HLA sensitization (*Local Consensus, 2020 [5]*).
- **Note 2:** These patients include:
  - **Heart:** Patients with single ventricle physiology, cardiac dysfunction, hypertrophic cardiomyopathy, restrictive heart disease
  - **Kidney:** Patients with Chronic Kidney Disease (CKD) stage 3 or higher (estimated GFR of < 60 ml/min/1.73 m<sup>2</sup>), on dialysis, under evaluation or waitlisted for kidney transplantation, have received a kidney transplant.
  - **Liver:** Patients who have received a liver transplant, underwent ATG/Campath induction, or are expected to be exposed to these T cell depleting therapies in the near future
  - **Lung:** Patients waitlisted for a lung transplant or who have received a lung transplant
  - **Small Bowel:** Patients waitlisted for small bowel transplant or who have received a small bowel transplant (*Local Consensus, 2020 [5]*).

## ALGORITHM FOR BLOOD PRODUCT ADMINISTRATION IN CHILDREN AND YOUNG ADULTS LIKELY TO NEED A SOLID ORGAN TRANSPLANT



### BACKGROUND

A difference in mental models concerning risks and benefits of blood product administration in children who are likely to require solid organ transplantation was identified as a root cause of a serious safety event at Cincinnati Children's Hospital. The purpose of this guideline is to provide a clear understanding of the risks and benefits of blood product administration in these patients and is likely to contribute to more accurate shared mental models and patient safety.

The decision to administer blood products requires careful consideration of all perceived risks and benefits in an individual patient (Scornik, 2013 [1a]; Fidler, 2013 [3b]; Eikmans, 2010 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Balasubramaniam, 2012 [4a]; Sanz, 2010 [4a]; Karpinski, 2004 [4a]; Togninalli, 2019 [4b]). The risks associated with blood product administration (specifically whole blood, platelets, and packed red blood cells) include HLA allosensitization in a minority of patients (Scornik, 2013 [1a]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Eikmans, 2010 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Lopes, 2015 [4a]; Pirim, 2015 [4a]; Balasubramaniam, 2012 [4a]; Sanz, 2010 [4a]; Karpinski, 2004 [4a]; Togninalli, 2019 [4b]; Picascia, 2016 [4b]). While efforts to leukoreduce blood products have decreased the risk of HLA allosensitization in some populations (Nelson, 2019 [2b]; Akgul, 2017 [4a]; Balasubramaniam, 2012 [4a]; Sanz, 2010 [4a]; Karpinski, 2004 [4a]), leukoreduction does not eliminate this risk (Nelson, 2019 [2b]; Fidler, 2013 [3b]; Balasubramaniam, 2012 [4a]; Sanz, 2010 [4a]; Karpinski, 2004 [4a]). However, the theoretical future risk of HLA allosensitization should not prevent or delay administration of blood products in patients with life threatening conditions that could be reversed by blood product administration (Local Consensus, 2020 [5]).

Studies using leukoreduced blood products, estimate that approximately 30% of patients will develop detectable anti-HLA antibodies after a single transfusion (Nelson, 2019 [2b]). This response may diminish with time in some patients (McKee, 2018 [3a]), but repeated sensitizing events (additional blood product administration, pregnancy, solid organ transplantation) increase the

rate of HLA allosensitization and the duration of detectable antibodies (Nelson, 2019 [2b]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Eikmans, 2010 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Lopes, 2015 [4a]; Pirim, 2015 [4a]; Togninalli, 2019 [4b]).

In the general healthy population, it is believed that HLA allosensitization does not pose significant risk to long-term health. However, in children or adults who may undergo solid organ transplantation in the future, HLA allosensitization has been associated with worse health outcomes in kidney and heart transplant recipients (Scornik, 2013 [1a]; Nelson, 2019 [2b]; McKee, 2018 [3a]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Akgul, 2017 [4a]) and is believed to contribute to worse outcomes in lung, small bowel and repeat liver transplant recipients (Local Consensus, 2020 [5]).

These adverse outcomes may include:

- increased waiting times (Balasubramaniam, 2012 [4a])
- increased risk of rejection
- decreased allograft survival
- increased mortality

(Scornik, 2013 [1a]; McKee, 2018 [3a]; Fidler, 2013 [3b]; Can, 2016 [4a]; Redfield, 2016 [4a]).

In children and adults awaiting liver transplantation, allosensitization does not appear to increase wait times (Del Bello, 2017 [4a]), but the impact of allosensitization on rejection rates and allograft survival is unclear.

## TARGET USERS FOR THE RECOMMENDATIONS

Clinicians (e.g. surgeons, physicians, anesthesiologists, nurse anesthetists, advance practice registered nurses (APRNs)) caring for patients likely to need a solid organ transplant and blood product(s).

Patients and families/caregivers

## EVIDENCE SYNTHESSES & DIMENSIONS FOR JUDGING RECOMMENDATION STRENGTH

### Care Recommendation Statement 1 (Strong)

It is strongly recommended that the theoretical future risk of allosensitization should not prevent or delay administration of blood products in patients with life threatening conditions that could be reversed by blood product administration (Local Consensus, 2020 [5]).

### Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 1

1. Safety / Harm (Side Effects and Risks)	<input type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input checked="" type="checkbox"/> Serious		
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal		
3. Burden on population to adhere to recommendation	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Unable to determine	<input type="checkbox"/> High		
4. Cost-effectiveness to healthcare system	<input type="checkbox"/> Cost-effective	<input checked="" type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective		
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates		
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative		
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)	<input checked="" type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○	<input type="checkbox"/> GNA*
<b>Overall Strength of the Recommendation:</b>	<input checked="" type="checkbox"/> <b>Strong</b>	<input type="checkbox"/> Moderate	<input type="checkbox"/> Weak	<input type="checkbox"/> Consensus	

Studies using leukoreduced blood products, estimate that approximately 30% of patients will develop detectable anti-HLA antibodies after a single transfusion (Nelson, 2019 [2b]). This response may diminish with time in some patients (McKee, 2018 [3a]), but repeated sensitizing events (additional blood product administration, pregnancy, solid organ transplantation) increase the rate of allosensitization and the duration of detectable antibodies (Nelson, 2019 [2b]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Eikmans, 2010 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Lopes, 2015 [4a]; Pirim, 2015 [4a]; Togninalli, 2019 [4b]).

In the general healthy population, it is believed that allosensitization does not pose significant risk to long-term health. However, in children or adults who may undergo solid organ transplantation in the future, allosensitization has been associated with worse health outcomes in kidney and heart transplant recipients (Scornik, 2013 [1a]; Nelson, 2019 [2b]; McKee, 2018 [3a]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Akgul, 2017 [4a]) and is believed to contribute to worse outcomes in lung, small bowel and repeat liver transplant recipients.

However, we reached unanimous consensus through a series of discussions that the above risks are future, theoretical risks that assume the patient survives and eventually meets requirements for transplantation, and therefore they should not take priority over actual risks of withholding blood products in life threatening situations.

### Care Recommendation Statement 2 (Strong)

It is strongly recommended that the decision to administer blood products requires careful consideration of all perceived risks and benefits in each individual patient (Scornik, 2013 [1a]).

- **Note 1:** This includes the risk of allosensitization, which has been associated with longer wait times and increased risk of rejection and mortality in patients who are in need of kidney or heart transplantation (Scornik, 2013 [1a]; McKee, 2018 [3a]; Ibrahim, 2011 [4a]).
- **Note 2:** While there is little published evidence on how pre-transplant allosensitization impacts the outcomes of lung and small bowel transplant recipients, it is likely that allosensitization is associated with longer wait times and increased risk of rejection and mortality in those patients. (Bond, 2000 [3a]; Gondolesi, 2006 [5b]).
- **Note 3:** Studies suggest that pre-transplant allosensitization does not impact primary liver transplant wait times but the impact of allosensitization on liver allograft outcomes (survival and rejection) is unclear (Del Bello, 2017 [4a]).

### Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 2

1. Safety / Harm (Side Effects and Risks)	<input type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input checked="" type="checkbox"/> Serious	
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal	
3. Burden on population to adhere to recommendation	<input type="checkbox"/> Low	<input checked="" type="checkbox"/> Unable to determine	<input type="checkbox"/> High	
4. Cost-effectiveness to healthcare system	<input checked="" type="checkbox"/> Cost-effective	<input type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective	
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates	
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative	
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)	<input checked="" type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○
<b>Overall Strength of the Recommendation:</b>	<input checked="" type="checkbox"/> <b>Strong</b>	<input type="checkbox"/> <b>Moderate</b>	<input type="checkbox"/> <b>Weak</b>	<input type="checkbox"/> <b>Consensus</b>

Studies using leukoreduced blood products, estimate that approximately 30% of patients will develop detectable anti-HLA antibodies after a single transfusion (Nelson, 2019 [2b]). This response may diminish with time in some patients (McKee, 2018 [3a]), but repeated sensitizing events (additional blood product administration, pregnancy, solid organ transplantation) increase the rate of allosensitization and the duration of detectable antibodies (Nelson, 2019 [2b]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Eikmans, 2010 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Lopes, 2015 [4a]; Pirim, 2015 [4a]; Togninalli, 2019 [4b]).

In the general healthy population, it is believed that allosensitization does not pose significant risk to long-term health. However, in children or adults who may undergo solid organ transplantation in the future, allosensitization has been associated with worse health outcomes in kidney and heart transplant recipients (Scornik, 2013 [1a]; Nelson, 2019 [2b]; McKee, 2018 [3a]; Resse, 2018 [3b]; Fidler, 2013 [3b]; Akgul, 2017 [4a]) and is believed to contribute to worse outcomes in lung, small bowel and repeat liver transplant recipients.

Through a series of meetings and discussion we reached unanimous consensus that in non-life-threatening situations there is to carefully weigh the risks and benefits of blood product administration including alternative therapies, prior to exposing the patient to the risk of allosensitization.

### Care Recommendation Statement 3 (Strong)

It is strongly recommended that transfusions for non-life-threatening events be done only after consultation with an appropriate solid organ transplant physician with the expectation that:

- both parties (primary care team and the solid organ transplant team) understand the risks versus benefits of a blood product administration (Local Consensus, 2020 [5])
- the appropriate preparation of the blood product will be specified by the transplant physician (Local Consensus, 2020 [5])

- the “primary service of record” will make the final decision of whether to administer or not administer the blood product (*Local Consensus, 2020 [5]*)
- decision on modality for optimization (pharmacologic versus blood transfusion) should be done in consultation with all stakeholders (admitting service, medical transplant service and if applicable surgical service, and anesthesia)

(*Scornik, 2013 [1a]; Nelson, 2019 [2b]; McKee, 2018 [3a]; Dzik, 2002 [3a]; Magee, 2012 [3b]; Akgul, 2017 [4a]; Del Bello, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Redfield, 2016 [4a]; Pirim, 2015 [4a]; Sanz, 2010 [4a]*).

### Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 3

1. Safety / Harm ( <i>Side Effects and Risks</i> )	<input type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input checked="" type="checkbox"/> Serious	
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal	
3. Burden on population to adhere to recommendation	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Unable to determine	<input type="checkbox"/> High	
4. Cost-effectiveness to healthcare system	<input type="checkbox"/> Cost-effective	<input checked="" type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective	
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates	
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative	
7. Grade of the Body of Evidence ( <i>See Evidence Table below; *GNA – Grade Not Assignable</i> )	<input checked="" type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○
<b>Overall Strength of the Recommendation:</b>	<input checked="" type="checkbox"/> <b>Strong</b>	<input type="checkbox"/> <b>Moderate</b>	<input type="checkbox"/> <b>Weak</b>	<input type="checkbox"/> <b>Consensus</b>

Recommending that transfusions for non-life-threatening events be done after consultation with an appropriate solid organ transplant representative likely poses minimal safety/harm risks as limiting “foreign” antigen exposure has been demonstrated to significantly lower the risk of developing anti-HLA antibodies (*Scornik, 2013 [1a]; Dzik, 2002 [3a]; Magee, 2012 [3b]; Redfield, 2016 [4a]; Sanz, 2010 [4a]*). As a result (of a lower panel reactive antibody), the wait time for transplantation is lower as is the risk for post-transplant antibody mediated rejection (*Del Bello, 2017 [4a]*). A (positive) consequence of the recommendation likely will improve both pre-transplant and post-transplant morbidity and mortality (*McKee, 2018 [3a]*). The burden on the (transplant) population is low due to the risk: benefit profile of not transfusing a patient for non-life-threatening events or lowering the risk of antigen exposure by selecting appropriate blood products (leukoreduced, HLA matched) (*Scornik, 2013 [1a]; Nelson, 2019 [2b]; Dzik, 2002 [3a]; Magee, 2012 [3b]; Akgul, 2017 [4a]; Can, 2016 [4a]; Guichard-Romero, 2016 [4a]; Pirim, 2015 [4a]; Sanz, 2010 [4a]*). This recommendation, by likely lowering the amount of transfusions per patient would be cost-effective. Although the body of evidence is only moderate, evident by the quality of the manuscripts reviewed (in the evidence table), the overall strength of the recommendation is strong.

### Care Recommendation Statement 4 (Strong)

It is strongly recommended that all surgical decision-making regarding blood transfusion, including the patient’s transfusion threshold take place in the operating room between the attending surgeon and anesthesiologist prior to each procedure and shared with the team (*Local Consensus, 2020 [5]*).

- Note 1:** For patients presenting for high risk procedures, blood products should be ordered prior to entering the operating room and available in the Haemobank prior to surgical incision (*Local Consensus, 2020 [5]*). (See appendix A for list of high-risk procedures)
- Note 2:** For patients presenting for intermediate or low risk procedures, discussion amongst surgery, medical transplant and anesthesia should occur regarding need for blood product preparation (*Local Consensus, 2020 [5]*). (See appendix A for list of intermediate and low risk procedures)
- Note 3:** Any procedure with an anticipated blood loss of  $\geq 7$  ml/kg should have a specific blood loss plan in place (*World Health Organization, 2009 [5b]*).
- Note 4:** A patient's risk overall for intraoperative bleeding is not purely based on planned procedure but is determined by the surgeon in coordination with the anesthesiologist and other members of the operative team. It should be a thoughtful synthesis of multiple factors including, but not limited to:
  - the patient’s size (and blood volume)
  - clinical condition
  - starting hemoglobin level



- comorbidities that inhibit clotting (renal failure, hepatic synthetic dysfunction, innate clotting disorder)
- medications that affect clotting and platelet function.

The frequency with which a particular procedure results in significant ( $\geq 7$  ml/kg) blood loss must be factored in, as well as the severity of bleeding for those times when it does occur. If a particular surgery rarely causes intraoperative bleeding, but the few times that it does may be of significant magnitude, or significant technical challenge to control (as in a subclavian vessel perforation or vena cava injury), such factors must be considered in estimating the patient's overall intraoperative bleeding risk (*Local Consensus, 2020 [5]*).

## Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 4

1. Safety / Harm ( <i>Side Effects and Risks</i> )	<input type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input checked="" type="checkbox"/> Serious		
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal		
3. Burden on population to adhere to recommendation	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Unable to determine	<input type="checkbox"/> High		
4. Cost-effectiveness to healthcare system	<input type="checkbox"/> Cost-effective	<input checked="" type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective		
5. Directness of the evidence for this target population	<input type="checkbox"/> Directly relates	<input checked="" type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates		
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative		
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)	<input type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○	<input checked="" type="checkbox"/> GNA*
<b>Overall Strength of the Recommendation:</b>	<input checked="" type="checkbox"/> <b>Strong</b>	<input type="checkbox"/> Moderate	<input type="checkbox"/> Weak	<input type="checkbox"/> Consensus	

Optimization of preoperative anemia and irradiation of packed red blood cells should not delay surgery for life-threatening conditions. Irradiation of blood products will be waived in a massive transfusion scenario. For patients presenting for major risk procedures, blood products should be ordered prior to entering the operating room and available in the Haemobank prior to surgical incision. For patients presenting for moderate or low risk procedures, discussion amongst surgery, medical transplant and anesthesia should occur regarding need for blood product preparation. The operating room presents a unique and dynamic environment and it is recommended that all decision-making regarding blood transfusion be shared between surgery and anesthesia. Blood product administration should proceed without delay in life threatening situations (*Local Consensus, 2020 [5]*).

## Transfusion Thresholds

### Care Recommendation Statement 5 (Strong)

It is strongly recommended that a restrictive transfusion threshold (Hgb  $\leq 7$ g/dL) be utilized for patients without other medical conditions that would dictate higher thresholds (*Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]*).

- **Note 1:** Restrictive transfusion thresholds (Hgb  $\leq 7$ g/dL) result in fewer transfusions and are noninferior (regarding mortality) to liberal transfusion thresholds (Hgb  $\geq 10$ g/dL) (*Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]*).
- **Note 2:** Restrictive transfusion triggers (Hgb 7- 8 g/dL) can be used for most patients (children and adults) (*Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]*).
- **Note 3:** Additional studies are needed to establish the blood count at which a blood transfusion is needed in patients who have suffered a heart attack or brain injury (*Carson, 2016 [1a]*).

### Care Recommendation Statement 6 (Strong)

It is strongly recommended that an intermediate hemoglobin concentration may justify a red blood cell transfusion based on:

- ongoing indication of organ ischemia
- potential or actual ongoing bleeding (rate and magnitude)
- patient's intravascular volume status
- patient's risk factors for complications of inadequate oxygenation
- low cardiopulmonary reserve and high oxygen consumption AND
- discussion with managing service

(*Carson, 2016 [1a]*).

## Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 5 and 6

1. Safety / Harm (Side Effects and Risks)	<input checked="" type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Serious		
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal		
3. Burden on population to adhere to recommendation	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Unable to determine	<input type="checkbox"/> High		
4. Cost-effectiveness to healthcare system	<input checked="" type="checkbox"/> Cost-effective	<input type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective		
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates		
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative		
7. Grade of the Body of Evidence <i>(See Evidence Table below; *GNA – Grade Not Assignable)</i>	<input checked="" type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○	<input type="checkbox"/> GNA*
<b>Overall Strength of the Recommendation:</b>	<input checked="" type="checkbox"/> <b>Strong</b>	<input type="checkbox"/> <b>Moderate</b>	<input type="checkbox"/> <b>Weak</b>	<input type="checkbox"/> <b>Consensus</b>	

Many of the studies demonstrated that restrictive transfusion thresholds result in fewer transfusions and therefore less exposures, conferring a health benefit to the patient (Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]). Studies have also demonstrated that restrictive transfusion thresholds are noninferior to liberal transfusion thresholds, therefore causing minimal harm to the patient (Carson, 2016 [1a]; Murphy, 2015 [2a]; Hajjar, 2010 [2a]; Lacroix, 2007 [2a]; Hébert, 1999 [2a]; Bell, 2005 [2b]). We are unable to determine the burden on the population to adhere to this recommendation. Because there are fewer transfusions with restrictive thresholds, this results in a cost savings to patient and institution. This evidence has been evaluated in the pediatric patient population. The evidence for these recommendations were grades 1a-2b and because of this received a high grade.

### Leukoreduction & Indications

#### Care Recommendation Statement 7 (Moderate)

It is recommended that all patients receive leukoreduced units (Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).

- **Note 1:** All red blood cells and platelets at Cincinnati Children’s are leukoreduced (Local Consensus, 2020 [5]).
- **Note 2:** Each unit of whole blood or unmodified red cells contains roughly 2 to 5 x 10<sup>9</sup> leukocytes. The most effective current leukocyte reduction filters ("third generation") can achieve a three- to four-log (99.9 to 99.99%) reduction, leaving residual leukocyte counts below 5 x 10<sup>6</sup>, and generally below 1 x 10<sup>6</sup> (Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).
- **Note 3:** Leukoreduction may help to decrease the following:
  - Febrile nonhemolytic transfusion reactions
  - Human leukocyte antigen (HLA) alloimmunization (Nelson, 2019 [2b])
  - Postoperative infection, bacterial contamination
  - Cardiac reperfusion injury

(Dzik, 2002 [3a]; Trial to Reduce Alloimmunization to Platelets Study Group, 1997 [3a]).

## Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 7

1. Safety / Harm (Side Effects and Risks)	<input checked="" type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Serious		
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal		
3. Burden on population to adhere to recommendation	<input checked="" type="checkbox"/> Low	<input type="checkbox"/> Unable to determine	<input type="checkbox"/> High		
4. Cost-effectiveness to healthcare system	<input checked="" type="checkbox"/> Cost-effective	<input type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective		
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates		
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative		
7. Grade of the Body of Evidence <i>(See Evidence Table below; *GNA – Grade Not Assignable)</i>	<input type="checkbox"/> High ⊕⊕⊕⊕	<input checked="" type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○	<input type="checkbox"/> GNA*
<b>Overall Strength of the Recommendation:</b>	<input type="checkbox"/> <b>Strong</b>	<input checked="" type="checkbox"/> <b>Moderate</b>	<input type="checkbox"/> <b>Weak</b>	<input type="checkbox"/> <b>Consensus</b>	

All red blood cells and platelets at CCHMC are leukoreduced. The recommendation that patients receive leukoreduced blood products is a default choice of blood product (excluding granulocyte units). All blood products received from our local blood supplier (Hoxworth Blood Center, Cincinnati, OH) are leukoreduced (Dzik, 2002 [3a]). It is how they are manufactured, and we do not receive units without leukoreduction. Leukoreduced products have less HLA molecules in

each unit, which is a preferable option for patients who should have as little HLA exposure as possible. Leukoreduction is cost-effective for reducing transfusion reactions and other health issues/side effects of blood transfusions but has not been demonstrated to completely prevent HLA alloimmunization (Nelson, 2019 [2b]).

## Irradiation and Indications

### Care Recommendation Statement 8 (Moderate)

It is recommended that Gamma or X-irradiation of cellular blood components (red cell, platelet, and granulocyte concentrates) be utilized to prevent TA-GvHD (a rare but almost invariably fatal complication of transfusion) (Local Consensus, 2020 [5]). However, irradiation of blood products should not delay blood product administration for life-threatening emergencies and will be waived in a massive transfusion (Local Consensus, 2020 [5]).

Utilize Gamma or X-irradiation of cellular blood components (red cell, platelet, and granulocyte concentrates) to prevent TA-GvHD in the following:

- blood products for intrauterine transfusion or neonatal exchange transfusion (Treleaven, 2011 [5a])
- blood products from first- or second-degree relatives and all HLA-selected components even if that patient is immunocompetent (Local Consensus, 2020 [5])
- for one year in the following
  - severe T-lymphocyte immunodeficiency syndromes – for life (Treleaven, 2011 [5a])
    - **Note:** A clinical immunologist should be consulted for advice in cases where there is uncertainty (Local Consensus, 2020 [5]).
  - patients undergoing allogeneic or autologous HSCT, starting at the time of initiation of conditioning chemotherapy, usually continued for life (Treleaven, 2011 [5a])
  - patients with Hodgkin lymphoma - for life (Treleaven, 2011 [5a])
  - patients treated with purine analogue drugs - for life (Treleaven, 2011 [5a])
  - patients who have been treated with anti-CD52 or ATG (Local Consensus, 2020 [5])
  - patients awaiting SOT with the peri-operative plan to use these T cell depleting agents (ATG/Campath) for induction of immunosuppression (Local Consensus, 2020 [5])
- indications may be extended more broadly in order to ensure coverage for all potential at-risk patients (Local Consensus, 2020 [5]).
- **Note:** Examples at CCHMC include:
  - All patients < 4 months of age, to protect patients with undiagnosed congenital immune deficiencies as well as patients receiving neonatal exchange transfusions (Local Consensus, 2020 [5]).
  - All patients receiving malignancy/cancer-related treatments (chemotherapy/radiation), to protect these patients against TA-GvHD risk (Local Consensus, 2020 [5]).
- **Note:** It is not necessary to irradiate fresh frozen plasma (FFP), cryoprecipitate, or fractionated plasma products (Treleaven, 2011 [5a]).

### Care Recommendation Statement 9 (Moderate)

It is recommended that children and young adults who have had solid organ transplantation or who are likely to require solid organ transplantation receive irradiated blood products (Local Consensus, 2020 [5]).

- **Note 1:** Preliminary data is not conclusive but suggests that irradiation of blood products may help to reduce HLA sensitization (Local Consensus, 2020 [5]).
  - **Note 2:** These patients include:
    - Heart: Patients with single ventricle physiology, cardiac dysfunction, hypertrophic cardiomyopathy, restrictive heart disease
    - Kidney: Patients with Chronic Kidney Disease (CKD) stage 3 or higher (estimated GFR of < 60 ml/min/1.73 m<sup>2</sup>), on dialysis, under evaluation or waitlisted for kidney transplantation, have received a kidney transplant.
    - Liver: Patients who have received a liver transplant, underwent ATG/Campath induction, or are expected to be exposed to these T cell depleting therapies in the near future
    - Lung: Patients listed for a lung transplant or who have received a lung transplant
    - Small Bowel: patients listed for small bowel transplant or who have received a small bowel transplant
- (Local Consensus, 2020 [5]).

## Discussion of the Dimensions and Synthesis of the Body of Evidence for Recommendation 8 and 9

1. Safety / Harm (Side Effects and Risks)	<input checked="" type="checkbox"/> Minimal	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Serious		
2. Health benefit to patient	<input checked="" type="checkbox"/> Significant	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Minimal		
3. Burden on population to adhere to recommendation	<input type="checkbox"/> Low	<input checked="" type="checkbox"/> Unable to determine	<input type="checkbox"/> High		
4. Cost-effectiveness to healthcare system	<input checked="" type="checkbox"/> Cost-effective	<input type="checkbox"/> Inconclusive	<input type="checkbox"/> Not cost-effective		
5. Directness of the evidence for this target population	<input checked="" type="checkbox"/> Directly relates	<input type="checkbox"/> Some concern of directness	<input type="checkbox"/> Indirectly relates		
6. Impact on quality of life, morbidity, or mortality	<input checked="" type="checkbox"/> Positive	<input type="checkbox"/> Moderate / Neutral	<input type="checkbox"/> Negative		
7. Grade of the Body of Evidence (See Evidence Table below; *GNA – Grade Not Assignable)	<input type="checkbox"/> High ⊕⊕⊕⊕	<input type="checkbox"/> Moderate ⊕⊕⊕○	<input type="checkbox"/> Low ⊕⊕○○	<input type="checkbox"/> Very Low ⊕○○○	<input checked="" type="checkbox"/> GNA*
<b>Overall Strength of the Recommendation:</b>	<input type="checkbox"/> Strong	<input checked="" type="checkbox"/> Moderate	<input type="checkbox"/> Weak	<input type="checkbox"/> Consensus	

For patients who meet criteria set forth in our guidelines, packed red blood cells and platelets should also be irradiated. It is not necessary to irradiate fresh frozen plasma (FFP), cryoprecipitate, or fractionated plasma products. The main guideline developed by Treleaven et al. (2011) used the GRADE system to make recommendations and grade the evidence regarding irradiation of blood products. Gamma or x-irradiation of blood components, by validated systems, is the recommended procedure to prevent TA-GVHD which has a mortality rate of 87-100% (Treleaven, 2011 [5a]). Therefore, the risk of not providing irradiated blood products to a recommended population is serious. Irradiation of blood products confers minimal risk to the patient and therefore low burden on the population to adhere to it. Irradiation of blood products is cost effective to prevent death due to TA-GVHD. Irradiation of blood products has been studied in pediatric and adult populations, including solid organ transplant populations. It is unclear at present whether irradiation of blood products will prevent allosensitization for children who will likely require solid organ transplantation, but from preliminary analysis of our own data it appears that this may be the case. Therefore, solid organ transplant programs at CCHMC have agreed to uniformly administer irradiated products to patients prior to transplant to study whether this will reduce allosensitization (Local Consensus, 2020 [5]).

## ABBREVIATIONS AND DEFINITIONS

### Abbreviations (if any)

APRNs - Advanced practice registered nurses  
 ATG - Anti-thymocyte globulin  
 CKD - Chronic Kidney Disease  
 ELM - Electronic Learning Module  
 ESKD - end-stage kidney disease  
 FFP - fresh frozen plasma  
 GFR - Glomerular filtration rate  
 Hgb - hemoglobin  
 HLA - human leukocyte antigens  
 HSCT - Hematopoietic Stem Cell Transplantation  
 IUT - intra-uterine transfusion  
 pRBC's - Packed Red Blood Cells  
 Plts - Platelets  
 rHuEPO - recombinant human erythropoietin  
 TA-GvHD - Transfusion-associated graft-versus-host disease

### Definitions

- Allosensitization – in this guideline refers to HLA allosensitization and is when a patient makes anti-HLA antibodies after a sensitization event (blood transfusion, pregnancy, solid organ transplant, immunization).
- Blood Product – Packed Red Blood Cells, Platelets, Fresh frozen plasma
- Solid Organ Transplant – kidney, heart, liver, small intestine, lung

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## IMPLEMENTATION PLAN

### Facilitators

- Each team representative will introduce, educate, and implement the guideline to their division/department in a manner appropriate for their area.
- Education regarding the guideline will be included in an ELM (Electronic Learning Module for orientation (new staff) and ongoing annual review (Safety College).
- Develop computer triggers that notify Blood Bank of patient's need for irradiated blood products

### Barriers

- Assuring house-wide education
- Development of computer system triggers to communicate to Blood Bank of patient's need for irradiated blood products

### Resource Implications

- House-wide dissemination to all clinical staff via Op-Ex
- Epic Flags
- ELM modules (education) and Safety College (annual review)

### Relevant CCHMC Tools

Patient Education Materials

Blood product order sets

CCHMC Transfusion Guidelines policy BB.TRG.901

ELM Learning Module: Epic – Blood Ordering and Management for Providers

Computer system triggers

### Outcome Measures

Safety reports and events involving solid organ transplant patients and blood

### Process Measures

Hgb 7 threshold compliance report

Discussion prior to surgery regarding possible blood transfusion

**CLINICAL QUESTIONS | SEARCH STRATEGIES | SEARCH RESULTS**

**CLINICAL QUESTIONS**

- 1**

**P** (Population) Among children and young adult patients who will likely need a solid organ transplant

**I** (Intervention) Does receiving blood products (pRBC, Plts or FFP)

**C** (Comparison) Compared to patients who do not receive blood products

**O** (Outcome) Increase the patient's risk of allosensitization?
  
- 2**

**P** (Population) Among children and young adult patients who will likely need a solid organ transplant

**I** (Intervention) Does receiving blood products (pRBC, Plts or FFP)

**C** (Comparison) Compared to not receiving blood products

**O** (Outcome) Increase allosensitization and long-term outcomes including time to transplant and allograft survival?
  
- 3**

**P** (Population) Among children and young adult patients who are likely to be candidates for a solid organ transplant who need to receive blood products (pRBC, Plt, or FFP)

**I** (Intervention) What intervention(s) including Blood Bank interventions

**C** (Comparison) Compared to no intervention(s)

**O** (Outcome) Decrease the risk of allosensitization?
  
- 4**

**P** (Population) Among children and young adult patients who are likely to be candidates for a solid organ transplant who may need to receive blood products

**I** (Intervention) What risks and benefits need to be articulated and balanced in the decision of administering blood products

**C** (Comparison) compared to not considering risks and benefits

**O** (Outcome) Decrease risk of allosensitization, time to transplantation, and allograft survival?

**Search Strategy**

To select evidence for critical appraisal for this Evidence Summary, the databases below were searched using search terms, limits, filters, and date parameters to generate an unrefined, "combined evidence" database. This search strategy focused on answering the clinical questions addressed in this document and employing a combination of Boolean searching on human-indexed thesaurus terms (e.g., MeSH) as well as "natural language" searching on words in the title, abstract, and indexing terms.

Search Databases	Search Terms	Limits, Filters, & Search Date Parameters	Date of Most Recent Search
<input checked="" type="checkbox"/> MedLine via PubMed or Ovid <input checked="" type="checkbox"/> CINAHL <input checked="" type="checkbox"/> Cochrane Database for Systematic Reviews <input checked="" type="checkbox"/> Google Scholar: <input checked="" type="checkbox"/> Reference Lists/Hand Searches	<ul style="list-style-type: none"> <li>• Solid organ transplant, kidney transplant Liver Transplantation / or liver transplant.mp</li> <li>Heart transplant Pretransplant Kidney transplant organ transplantation</li> <li>• Blood Product or blood product transfusion Blood Transfusion / or Blood Component Transfusion / or Platelet Transfusion / or transfusion.mp. Irradiated blood irradiation or Irradiate or Irradiation gamma irradiated blood, Irradiated Packed Red Blood Cells</li> <li>• Immunosuppressive agent, immunosuppression</li> <li>• Mycophenolic Mycophenolic acid HLA Antigens / or panel reactive antibody.mp. or Histocompatibility Testing</li> </ul>	Publication Dates or Search Dates: <ul style="list-style-type: none"> <li>• 01/1946 to 03/16/2020</li> </ul> <input checked="" type="checkbox"/> English Language <input checked="" type="checkbox"/> Primarily pediatrics but included young adult literature as applicable <input checked="" type="checkbox"/> Other Limits or Filters: <ul style="list-style-type: none"> <li>• Human</li> </ul>	03/16/2020

## Search Results

The citations were reduced by eliminating duplicates, review articles, non-English articles, and adult articles (e.g., limits/filters above). The resulting abstracts and full text articles were reviewed by a methodologist to eliminate low quality and irrelevant citations or articles. Two team members reviewed and appraised "full text" of identified studies for reliability, validity, and applicability. During the course of the guideline development, additional articles were identified from subsequent refining searches for evidence, clinical questions added to the guideline and subjected to the search process, and hand searching of reference lists. The dates of the most recent searches are provided above.

The electronic and manual searches for evidence identified 283 articles.

Two hundred and twenty-nine articles were discarded, as they were duplicates, or not related to the clinical question of interest based on title and abstract review.

Fifty-four articles were reviewed in full text and critically appraised. Twenty-one articles were excluded/discarded following full text review due to not related to clinical questions or methodologically sound

Thirty-three articles met the inclusion criteria above and are referenced in the guideline.

## TEAM MEMBERS & CONFLICTS OF INTEREST

### Group / Team Members

#### *Multidisciplinary Team*

##### Team Leader/Author:

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Jennifer Chamberlin, Specialist Parent Program

##### Support/Consultants:

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### *Other Evidence-Based Care Recommendation Development Support*

##### Methodologist:

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##### Content Reviewers:

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Laura Flesch, APN, Bone Marrow Transplant, Cincinnati Children's Hospital

### Conflicts of Interest were declared for each team member and:

No financial or intellectual conflicts of interest were found.

Conflict of interest declaration information is maintained in Cincinnati Children's ePAS (*electronic Protocol Administration System*).

## External Funding

No external funding was received for development of this recommendation. Recommendations were developed through hospital funding via salaries.

## EVIDENCE-BASED CLINICAL CARE RECOMMENDATION DEVELOPMENT PROCESS

The process by which these recommendation statements were developed is documented in the [Guideline Development Process Manual](#); relevant development materials are kept electronically. The recommendations contained in this guideline were formulated by a multidisciplinary working group, which performed a systematic search and critical appraisal of the literature using the LEGEND Evidence Evaluation System (see next section below).

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference, and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

### LEGEND Evidence Evaluation System (Let Evidence Guide Every New Decision)

#### Evidence Levels of Individual Studies by Domain, Study Design, & Quality ([Link to Full Table](#)):

Individual studies are appraised for reliability, validity, and applicability, using standardized appraisal forms, to determine the quality level or Evidence Level (a vs b)<sup>†</sup>.

Quality Level	Definition
1a <sup>†</sup> or 1b <sup>†</sup>	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

<sup>†</sup>a = good quality study OR b = lesser quality study

#### Grade for the Body of Evidence ([Link to Full Table](#)):

The Body of Evidence (BOE) is evaluated for quantity, quality, and consistency to determine the grade of the BOE and what the impact of the BOE is on our confidence in the precision of the answer to the clinical question (and its associated recommendation statement).

Grade	Definition
High	Good quality, High-level studies with consistent results
Moderate	Good quality, Lower-level or Lesser quality, Higher-level studies with consistent* results
Low	Good or lesser quality, Lower-level with results that may be inconsistent
Very Low	Few Good or Lesser quality, Low-level studies that may have inconsistent results
Grade Not Assignable	Local Consensus

#### Dimensions for Judging the Strength of the Recommendation ([Link to Full Table](#)):

1. Safety / Harm	5. Directness of the Evidence
2. Benefit to Target Population	6. Impact on Quality of Life, Morbidity, or Mortality
3. Burden on Population to Adhere to Recommendation	7. Grade of the Body of Evidence
4. Cost-Effectiveness for the Healthcare System	

#### Language and Definitions for Recommendation Strength ([Link to Full Table](#)):

Language for Strength	Definition
It is strongly recommended that... It is strongly recommended that... not...	When the dimensions for judging the strength of the recommendation are applied ( <i>including safety/harm, health benefit, body of evidence, etc.</i> ), there is high support that benefits clearly outweigh risks and burdens. ( <i>or visa-versa for negative recommendations</i> )
It is recommended that... It is recommended that... not...	When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.
It is suggested that... It is suggested that... not...	When the dimensions for judging the strength of the evidence are applied, there is weak support that benefits are closely balanced with risks and burdens.
There is insufficient evidence to make a recommendation...	



## Review Process

This guideline has been reviewed against quality criteria by at least two independent reviewers from Cincinnati Children's including, but not limited to, evidence methodologists, relevant subject matter experts, or other stakeholders who were not involved in the development process.

### – Reviewer Comments

All feedback received from reviewers was appropriately discussed and acted upon by the development team.

The guideline was also externally appraised by three independent reviewers not involved in the development process using the **AGREE instrument** (*Appraisal of Guidelines for Research and Evaluation*) and the results by domain are:

- Scope and Purpose 69 %
- Stakeholder Involvement 83 %
- Rigor of Development 84 %
- Clarity and Presentation 100 %
- Applicability 94 %
- Editorial Independence 100 %

## Revision Process

The guideline will be removed from the Cincinnati Children's website, if content has not been revised within five years from the most recent publication date. A revision of the guideline may be initiated at any point within the five year period that evidence indicates a critical change is needed. Team members reconvene to explore the continued validity and need of the guideline.

## Review History

Date	Event	Outcome
Oct. 2020	Original Publication	New Evidence-based Guideline developed and published

## Permission to Use the Guideline

This Evidence-Based Care Guideline (EBCG) and any related implementation tools (*if applicable, e.g., screening tools, algorithms, etc.*) are available online and may be distributed by any organization for the global purpose of improving child health outcomes.

Website address: <http://www.cincinnatichildrens.org/service//anderson-center/evidence-based-care/recommendations/default/>

Examples of approved uses of the EBCG include the following:

- Copies may be provided to anyone involved in the organization's (*outside of Cincinnati Children's*) process for developing and implementing evidence-based care recommendations;
- Hyperlinks to the Cincinnati Children's website may be placed on the organization's website;
- Evidence-Based Care Recommendations may be adopted or adapted for use within the organization, provided that Cincinnati Children's receives appropriate attribution on all written or electronic documents; and
- Copies may be provided to patients and the clinicians who manage their care.

Notification to Cincinnati Children's ([EBDMInfo@cchmc.org](mailto:EBDMInfo@cchmc.org)) is appreciated for all uses of any EBCG or its companion documents which are adopted, adapted, implemented, or hyperlinked.

## Please cite as

Hooper, D; Amin, A; Rosen, N; Nathan, J; Chin, C; Huff, J; Kinney, S; Loses, M; Miethke, A; Schechter, M; Vonderhaar, K (2020). Cincinnati Children's Hospital Medical Center: **Evidence-based Guideline: Evidence-Based Guideline for Blood Product Administration in Children and Young Adults Likely to Need a Solid Organ Transplant.** <http://www.cincinnatichildrens.org/service//anderson-center/evidence-based-care/recommendations/default/>, Evidence-based Guideline 50, pages 1-36, 2020. *Hyperlink the document.*

## For more information

About this guideline, its companion documents, or the Cincinnati Children's Evidence-Based Care Recommendation Development process, contact the Cincinnati Children's Evidence Collaboration at [EBDMInfo@cchmc.org](mailto:EBDMInfo@cchmc.org).

## Note/Disclaimer

This guideline addresses only key points of care for the target population; it may not be a comprehensive practice guideline. These care recommendations result from review of literature and practices current at the time of their formulations. This guideline does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This

document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this guideline is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding any specific care recommendation.

## APPENDIX A *Risk Classification of Operating Room Procedures*

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**All surgical decision-making regarding blood transfusion in the operating room, including the patient's transfusion threshold, should be shared between the attending surgeon and anesthesiologist, and discussed prior to each procedure.**

- Blood product administration should proceed without delay in life threatening situations.
- For patients presenting for major risk procedures, blood products should be ordered prior to entering the operating room and available in the Haemobank prior to surgical incision.
- **High risk procedures include but not limited to:**
  - Major open abdominal surgery
  - Cardiac surgery
  - Tumor resection
  - Major neurosurgical procedure
  - Major orthopedic procedure
  - Thoracotomy
  - Neonatal/infant emergency procedure
  - Trauma
  - Major gynecologic/urologic procedures
  - Burns
  - Major ENT surgery (airway reconstruction, tumor resection, etc)
  - HD/apheresis line placement or exchange in children weighing < 10kg
- For patients presenting for moderate or low risk procedures, discussion amongst surgery, admitting service of record, and anesthesia should occur regarding need for blood product preparation.
  - **Intermediate risk procedures include but not limited to**
    - Laparoscopic surgery
    - Thoracoscopic surgery
    - Robotic surgery
    - Minor open abdominal surgery
    - HD line placement or exchange in children weighing  $\geq 10$  kg
    - Tumor biopsy
    - Minor gynecologic procedure
    - Central line/port placement (initial line; non-HD/apheresis) in babies (< 5kg)
    - Central line/port placement in a child with history of prior central venous lines
  - **Low risk procedure procedures include but not limited to**
    - Minor ENT surgery (BMT, T&A, etc)
    - Central line/port placement in children weighing  $\geq 5$ kg, initial line, or Non-HD/apheresis
    - IR procedure
    - Endoscopic procedures
    - Minor Urologic procedures
- **Any procedure with an anticipated blood loss of  $\geq 7$  ml/kg should have a specific blood loss plan in place.**

(Local Consensus, 2020 [5])

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