1. Cover Page containing the following information:
   • Hospital or Healthcare System name and address, city, state, URL.
     ◦ UC Irvine Health Medical Center, 101 The City Dr S, Orange, CA
     ◦ http://www.ucirvinehealth.org
   • Name, title, e-mail address and phone number for a contact person.
     ◦ Minh-Ha Tran, DO; minhhat1@uci.edu; 714-456-8925
     ◦ William C Wilson MD; wcw@uci.edu; 714-456-7455
   • Name, e-mail address and phone number of the contact person’s assistant, if applicable.
     ◦ Cindy Merino; cmerino@uci.edu; 714-456-5067
   • Title of application.
     ◦ Quality Improvement in ICU Blood Utilization
   • Identify topical area(s) of focus in this application:
     ◦ patient safety
     ◦ quality improvement
   • Brief statement by an executive leader in support of the application.

2. Executive Summary (limit 200 words)

Blood transfusion has been identified by Joint Commission and AABB (Advancing Transfusion and Cellular Therapies Worldwide) as a key area of focus in healthcare quality improvement. Patients requiring Intensive Care Unit (ICU) admission have the highest likelihood of transfusion. The weight of the medical literature is now supporting more restrictive transfusion thresholds resulting in increased scrutiny around blood transfusion decisions. The UCI Critical Care program developed and implemented a high-level blood transfusion guideline whose primary aim was to communicate principles of evidence-based transfusion practice. In so doing, a 24% reduction in transfusion cost/patient was realized without compromising patient safety.

3. Background and relevance of the problem being addressed and effort undertaken

Increasing scrutiny has been placed upon transfusion practices. Recognizing and reducing unnecessary transfusions addresses parallel goals of improving both quality and cost-effectiveness while reducing transfusion-associated risks. Furthermore, blood utilization in general is subject to significant heterogeneity in
practice patterns. In the ICU, where as many as 44.1% of patients can require transfusion\(^1\), we sought to homogenize transfusion practices in an effort to improve quality of care.

4. Describe the effort, including the scope, process, strategies and tactics utilized, challenges encountered and how they were addressed.

A multi-disciplinary task force was formed under the leadership of our Intensive Care Unit Director. Representation from acute-care surgery, neurosurgery, neuro-critical care, pulmonary-critical care specialists, critical-care pharmacy, transfusion medicine, and nursing staff ensured highest likelihood for buy-in and clinician adoption.

The literature was reviewed and incorporated, specialty-specific best-practices reviewed, and input from experts sought in the development of an ICU Blood Utilization Guideline (See Attachment 1). Drafts received additional reviews at multiple levels through key hospital committees thus arriving at final approval through critical care committee, medical executive committee, and governing body advisory committee.

The guideline was rolled out in August of 2014 and became the basis for transfusion decisions in ICU patients thereafter. Efforts were applied in a top-down manner through decision-making during clinical rounds.

5. Describe the results of the effort.

Data on blood utilization were obtained through decision support. All charges associated with any blood component transfusion taking place in any adult ICU were tabulated as Cost/Patient and analyzed over a 15-month period (Q1 15 through Q1 16) following implementation.

The results demonstrate steady reduction in blood utilization across all intensive care units, culminating in nearly a 25% reduction cost/patient for blood products throughout the analyzed period (see Figure 1).
6. Discuss the significance of the results. How do the results demonstrate outstanding achievement?

Murphy and colleagues report results of a multi-faceted quality improvement program designed to decrease, among other things, RBC utilization in ICU. Through dissemination of best-practices and financial incentives to the units for meeting predefined targets. RBC utilization declined by 17% in the post-implementation period.

Wahl and colleagues report results following implementation of a transfusion guideline in a trauma-burn ICU. Prior to implementation, a 26% rate of blood transfusions was observed during a 9-month prospective observation period (8/03 – 4/04). To judge sustainability of their intervention, the proportion of patients transfused during 2005 was assessed, yielding an 18% rate, or 31% reduction.

In our study, we used hospital financial reporting as a surrogate for blood utilization. We feel this is a reasonable methodology given that hospital cost per
unit and mix of vendor derived vs internally collected units was relatively constant throughout the analyzed period.

Reductions realized following implementation of our guideline are therefore in line with achievements published by other groups. In addition, reduced blood utilization did not adversely impact mortality rates or ICU length of stay.

7. Describe sustainability and scaling of the achievements.

Given that the analysis period began some months following implementation, we feel the continued downward trend over time is indicative of a sustained response.

For the analyzed period, a cost per patient savings of ($4587 - $3480 =) $1107 was realized. Our data additionally demonstrate a continued trend toward reduced utilization.

8. Describe key lessons learned and any advice to colleagues who might try to undertake a similar effort.

This process has generated a number of lessons-learned that may be useful to others in their efforts to control blood utilization.

- **Identify an influential and committee Champion.**
  - In our case, Dr. William Wilson, our ICU Director, successfully convened our team and kept efforts on track. He also successfully carried out implementation of the end-product and ensure continued adherence.

- **Empanel a multidisciplinary team of involved clinician-stakeholders.**
  - Involving key providers whose patients are directly impacted by the guideline ensured ease of adoption and buy-in by our specialists.

- **Seek review and approval by key hospital committees.**
  - This process further ensures breadth of multidisciplinary review. It also more widely communicates important quality improvement initiatives as various members take this work back to their respective areas. Finally, approval by high-level committees formalizes the guideline and establishes it as ‘standard practice’, thus further
facilitating buy-in and adherence.

- **Provide education to end-users of the guideline.**
  
  o In our case, this was facilitated on daily ICU rounds by attending staff and through case-by-case discussion of patient transfusion needs. The guideline provided a framework for these discussions.

References


Please limit the sections 3-8 to a total of 2,400 words.

Applicants are welcome to upload any supplementary material in support of their application, such as graphics, data displays, photographs.
ICU Blood Utilization Guideline

Executive Summary

- This document conveys UCI Critical Care Committee guidelines toward transfusion for adult ICU patients. For the purposes of this document, adults are defined as those ≥14 y/o or ≥40 kg.

- For red cell transfusion therapy, current evidence and major guideline statements support a restrictive threshold of <7 g/dL prior to consideration of transfusion therapy in otherwise stable ICU patients without acute coronary syndrome (ACS).

- Reported transfusion thresholds represent basic guidelines; not hard endpoints – individualize transfusion decision-making to optimize benefit while reducing transfusion-related risks.

- Bleeding patients, especially those becoming hemodynamically unstable, require immediate resuscitation and a low threshold for involvement of surgical or other interventional specialists.

- Following transfusion, assess for anticipated response (ie, resolution of bleeding or expected increment in target laboratory marker); consult blood bank if transfusions are not resulting in expected responses.

Introduction

A successful patient blood management program reduces unnecessary transfusion while maintaining patient safety. This guideline aids clinicians in transfusion decision-making.

Priorities:

- Reduce heterogeneity in transfusion practice by forwarding an approved transfusion guideline

- Identify and reduce excessive or unnecessary transfusions among otherwise stable patients
**Background**

Patients with declining hemoglobin values and clinical signs of anemia (such as tachycardia, hypotension, mental status changes or other signs of hypoperfusion) may benefit from red blood cell (RBC) transfusion. Not all forms of hemodynamic instability are transfusion remediable. Non-RBC transfusions are more difficult to justify, particularly in the absence of frank bleeding. Furthermore, routine coagulation tests are poorly predictive of bleeding risk\(^1\), and ‘correction’ of these values with transfusion therapy does not guarantee hemostasis.

Iatrogenic anemia is a major issue in hospitalized patients and laboratory testing contributes to lower prevailing hemoglobin levels and enhanced transfusion risk without apparent benefits in outcomes\(^2\). However, erythroid stimulating agents have not been shown to confer a strong blood avoidance benefit in critical care patients and routine use should be avoided\(^3\). Laboratory testing should therefore be guided by clear, patient-centered indications. The use of smaller volume collection tubes will aid in reducing the impact of phlebotomy related iatrogenic anemia, but more judicious test ordering is also an important component.

A number of randomized controlled trials support recent guidelines from the AABB (Advancing Transfusion and Cellular Therapies Worldwide)\(^4\) and the American Board of Internal Medicine’s Choosing Wisely Campaign\(^5\) (via the American Society of Hematology) supporting restrictive transfusion thresholds (<8 g/dL with avoidance of arbitrary transfusion triggers and a practice geared toward transfusion of the minimal number of units required to stabilize the patient).

Among randomized trials, restrictive transfusion strategies have been strongly associated with reduced risk of Healthcare Associated Infection (HAI). A recent meta-analysis\(^6\) demonstrated a reduced relative risk of 0.82 [95%CI 0.72 to 0.95 with little heterogeneity] of serious HAIs for patients randomized to restrictive hemoglobin transfusion thresholds with a Number Needed to Treat [with a restrictive threshold] of only 38 to avoid one major HAI.

According to a recent prospective study\(^7\), the risk of Transfusion Associated Circulatory Overload (TACO) may be as high as 1:68 [95% CI 1:250 to 1:27], whereas Transfusion Related
Acute Lung Injury (TRALI) has become less frequent (1:12,000\(^4\)) with modern donor deferral practices for high-risk donors. Patients with edematous states and organ failure are at particular risk for TACO.

Plasma is frequently transfused prophylactically in non-bleeding patients with abnormal coagulation values about to undergo invasive procedures. This practice is not supported by a strong evidence base and two, large, meta-analyses\(^8,9\) have demonstrated no benefit from prophylactic plasma transfusion. In the setting of mildly prolonged INR values (ie, <1.8) retrospective studies evaluating pre- and post-transfusion INR (delta INR) demonstrate minimal, if any, INR with FFP transfusion correction\(^10,11\). Furthermore, the duration of effect of FFP upon the INR is limited (~8 hours)\(^12\) therefore, in warfarin-treated patients in whom Vitamin K is not included as a part of the initial reversal protocol, the phenomena of warfarin rebound must be guarded against.

Transfuse platelets and cryoprecipitated Anti-Hemophilic Factor (CRYO) based upon pretransfusion platelet counts and fibrinogen levels, respectively, whenever possible. Obtain post-transfusion follow up levels within one hour of transfusion and evaluate the patient for response (ie, cessation or stabilization of bleeding). Patients not demonstrating expected increments (see below) warrant further evaluation for refractoriness.

**RBC Transfusion Guideline**

A decision model based upon clinical indicators is recommended. RBC transfusion is not always indicated for hypoperfusion states, and other non-blood resuscitation fluids as well as vasopressor and inotropic agents are available.

Anemia is a sign rather than a diagnosis, and its etiology should be elucidated. Assess for risks of nutritional or iron deficiency in anemic patients, iron replacement can take place via oral or parenteral routes. Sites of active bleeding may require surgical, endoscopic, or endovascular management.
In a non-bleeding patient with declining hemoglobin, considerations also include hemodilution and hemolytic transfusion reaction. Testing for hemolysis includes measuring levels of LDH, Bilirubin (Total and Direct), Haptoglobin, and Direct Antiglobulin Test (DAT).

Ideally, transfusion practice is patient-centered rather than simply hemoglobin based, but current data supports utilization of a threshold < 7 g/dL for most critically ill patients with associated clinical indications. A standard adult RBC transfusion dose is 1 Unit. Reassess the patient following transfusion for markers of response.

Be conscious of phlebotomy draws and their contribution to iatrogenic anemia. Strive to consolidate laboratory draws and to avoid redundant laboratory testing.

Quest ordering alerts are of interest in reducing unnecessary blood product ordering, including alerts that call attention to most recent Hemoglobin levels (ie, alert if Hb > 10 g/dL) and orders for 2 or more units of blood (ie, arbitrary 2 unit orders). Providers will be asked to attest to bleeding or other instability prior to proceeding.

**Non RBC Blood Product Transfusion Guidelines**

Plasma, platelets, and cryoprecipitate may be transfused prophylactically (in a non-bleeding patient with laboratory coagulopathy) or therapeutically (a bleeding patient with laboratory coagulopathy). The latter scenario is more readily justifiable based upon evidence-based practice.

In non-anticoagulated patients without a history of bleeding diathesis, the results of routine tests of coagulation are poorly predictive of subsequent bleeding events. Transfusing against a simple ‘laboratory’ trigger in a nonbleeding patient may therefore expose the patient to unnecessary transfusion and its associated risks.
Certain scenarios may better justify transfusion support. The following examples are illustrative:

1) Warfarin Reversal in a bleeding patient:
   a. Options: Plasma, Prothrombin Complex Concentrate, Vitamin K (PO/IV)

2) Bleeding in the setting of abnormal coagulation parameters:
   a. Rising INR (Typically > 2.0):
      i. Options: Same as for 1a
   b. Thrombocytopenia (Typically < 50 K/mcL):
      i. Platelet transfusion (schema = 1 apheresis platelet unit, assess for response)
      ii. In certain circumstances, qualitative platelet defects may justify platelet transfusions at higher platelet thresholds in the setting of critical-site or life-threatening bleeding.
   c. Hypofibrinogenemia (Typically < 110 mg/dL):
      i. Cryoprecipitate (transfuse 20 Units, assess for response), consider antifibrinolytics if hyperfibrinolysis is suspected

Acquired qualitative platelet defects include those induced by medications (Thienopyridines – clopidogrel, prasugrel, ticagrelor; GP IIb/IIIa inhibitors – Abciximab, Integritin) or underlying illness (severe uremia). Options for treatment of qualitative platelet defects include postponing (if possible) the procedure until 5-7 days have elapsed following cessation of oral antiplatelet therapy or administration of hemodialysis, DDAVP, conjugated estrogens, or other modalities prior to high-risk procedures in patients with significant uremia. Patients may also have hereditary bleeding disorders thus emphasizing the importance of obtaining a bleeding history.

Certain situations (ie, intracranial hemorrhage) may justify more aggressive transfusion support and transfusion at less severe parameters. A 1-hour post-transfusion platelet count is recommended for assessment of increment.

In general, non-RBC and hemostatic use is aimed toward combined clinical and laboratory responses. Nonattainment of expected laboratory responses requires reassessment to ensure the correct diagnosis is being addressed (ie, continued prolongation of PT, PTT in a massively
resuscitated patient: nonresponse in INR following Plasma/PCC should elicit measurement of fibrinogen level rather than continued dosing of non-CRYO products).

For non-anticoagulated patients undergoing neuraxial anesthesia with isolated thrombocytopenia, a platelet count of 80 K/mcL is generally considered safe; for the same patient requiring lumbar puncture, a count of 40 K/mcL is generally considered safe\(^\text{14}\) although large series\(^\text{15,16}\) have demonstrated safety for lumbar puncture at more severe degrees of thrombocytopenia.

Central venous catheter placement, particularly in the current of era of bedside ultrasound, can generally proceed in non-anticoagulated patients with stable coagulopathies (ie, elevated INR, thrombocytopenia)\(^\text{17,21}\).

In the setting of chronic, compensated, end-stage Liver Disease (ESLD), previous assumptions held that prolongations of PT, INR, and PTT in addition to the common finding of thrombocytopenia in such patients portended bleeding risk. Newer, evidence-based attitudes support a ‘rebalanced hemostasis’ model which more easily may be tipped toward either a hemorrhagic or thrombotic phenotype compared to healthy individuals but which, nonetheless, is capable of relatively normal hemostasis\(^\text{22}\). In fact, excessive transfusion may contribute to increased central venous pressure in such patients, a scenario that does increase bleeding risk. Restrictive transfusion strategies and appropriate, pharmacologic Venous Thromboembolism (VTE) prophylaxis remains indicated in most patients with ESLD\(^\text{23}\).

Coagulopathy is not uncommon among ICU patients. Thrombocytopenia may be observed in up to 68% of patients upon admission and in 13%-44% of patients during their ICU stay\(^\text{24}\). The etiology is frequently multifactorial and includes sepsis, Disseminated Intravascular Coagulation (DIC), drugs, bleeding, hypersplenism, and cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO). Drug-Induced Immune Thrombocytopenia is frequently associated with severe degrees of thrombocytopenia (ie, single-digit ranges) and bleeding phenotype, whereas Heparin Induced Thrombocytopenia (HIT) is characterized by less severe degrees (50 to 80 K/mcL, rarely < 20 K/mcL) of thrombocytopenia and a thrombogenic phenotype. Immune Thrombocytopenia (ITP) is typically a pre-existing diagnosis in
hospitalized patients and is characterized by isolated thrombocytopenia (unless bleeding or medications have affected other cell lines). Platelet transfusion is typically ineffective in patients with ITP and alternatives such as steroids and Intravenous Immune Globulin (IVIG) are preferred. For cancer and hematologic malignancy patients with otherwise stable, hypoproliferative thrombocytopenia related to chemotherapy a platelet counts in the 10 to 20 K/mcL range have been found to be safe for prophylactic transfusions. High risk scenarios, including fever, major infection, sepsis, recent (ie, within the last 2-4 weeks) major bleeding or anticipated surgery may justify higher transfusion thresholds in these patients.

Patients with INR 1.5 to 3.0 are frequently transfused plasma prophylactically prior to procedures. The recently published TOPIC (Transfusion Of FFP in non-bleeding ICU patients) trial was prematurely stopped due to slow enrollment. As such, the study did not meet a-priori sample size criteria of 200 patients per arm. Patients with INR 1.5 to 3.0 were randomized to receive FFP (12 mL/kg; n=38) or not (n=38) prior to insertion of CVC, thoracocentesis, percutaneous tracheotomy, drainage of abscess or fluid collection. Occurrence of bleeding (minor or major) during or within 24 hours following procedure did not differ between groups. Furthermore, although the median INR reduction (from 1.8 (IQR 1.5-2.5) to 1.4 (IQR, 1.3-1.63) was significant, FFP infusion resulted in correction of INR to < 1.5 in only 54% of patients. Patients with higher pretransfusion INR values experienced the greatest reduction after FFP transfusion.

In a retrospective analysis of ICU patients, 44/115 (38.3%) nonbleeding patients with INR > 1.5 received FFP transfusion. The INR was corrected in only 16/44 (36%) transfused patients. Although there was no difference in new bleeding episodes between the transfused and non-transfused groups (6.8% vs 2.8%, respectively, p=0.369), new onset acute lung injury was more frequent in the transfused group (18% vs 4%, respectively, p=0.021). The authors concluded that the risk-benefit ratio of FFP transfusion among critically ill patients with stable coagulopathy may not be favorable.
Table 1: Coagulopathy in ICU Patients

<table>
<thead>
<tr>
<th>Laboratory Condition</th>
<th>Stable (Unchanging)</th>
<th>Unstable (Changing)</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Platelet Count (K/mcL) | 20 – 40 | Progressive decline | Transient reductions in the platelet count following clinical insults (Cardiopulmonary Bypass Surgery, Cardiac Arrest, Acute Decompensation due to Sepsis or other Illness) with attainment of new, lower mean levels is not uncommon. In the absence of active bleeding or high-risk features (such as intracranial hemorrhage), thrombocytopenia tolerance is reasonable since treatment of the underlying disease process and clinically improvement will typically be associated with recovery of platelet counts.

Progressively declining platelet counts may occur in the setting of DIC (in which schistocytosis and declining fibrinogen levels may also be noted) and decompensated ESLD. Rarely, drug-induced immune thrombocytopenia may also be an issue.

In the setting of pancytopenia, immune thrombocytopenia, leukemia, or other hematologic malignancy or concern, hematology consultation is advised. |
| INR | 1.5 to 2.5 | Progressive prolongation | Stable, mild elevations of the INR in non-bleeding patients are generally well-tolerated. When anticoagulation is not desired, Vitamin K may be an option. Aggressive FFP transfusion in the otherwise stable, non-bleeding patient is typically unwarranted. Patients with compensated ESLD remain capable of hemostasis (and thrombosis) and INR prolongations within the patient’s overall baseline range should not trigger aggressive FFP transfusion in the absence of bleeding. Treatment of DIC is aimed at identification and treatment of the underlying driver.

Progressive prolongation of INR may be seen with certain anticoagulants, dilutional coagulopathy, decompensated ESLD, and DIC. Transfusion becomes indicated when bleeding develops or the severity of the derangement combined with underlying comorbidities raise concern for major bleeding. |
| Isolated prolongation of PTT (seconds) | INR normal PTT < 1.5 x ULN | >3xULN | In a patient without hemophilia, significant, isolated prolongation of the PTT is suggestive for heparin contamination (ie, from a line draw) or supratherapeutic heparin effect. Argatroban and Bivalirudin are also monitored using the PTT. Discuss management with critical care pharmacist and attending staff. |
| Fibrinogen (mg/dL) | >110 mg/dL | Progressive Decline | Most authorities consider levels of 50 to 100 mg/dL sufficient for hemostatic competence in most patients. Progressive decline and severe reductions (<50 mg/dL) may produce concomitant prolongation of the PT (INR) and PTT given the position of fibrinogen in the common pathway.

Progressive decline in fibrinogen may be seen in the setting of dilutional coagulopathy, DIC, hyperfibrinolysis (typically in the setting of decompensated ESLD) and as a transient finding following administration of recombinant Tissue Plasminogen Activator (r-TPA). Hypofibrinogenemia may also be an artifactual finding in patients treated with direct thrombin inhibitors. Transfusion of Cryoprecipitate becomes indicated in the setting of bleeding or high-risk features combined with severe hypofibrinogenemia (<110 mg/dL). |

ULN = Upper Limit of Normal. For additional information regarding specific blood components and expected transfusion responses, see the Blood/Blood Component Transfusion Policy found at: https://start.hs.uci.edu/sites/policiesandprocedures/hospital/Patient%20Care%20Policies/Blood.%20Blood%20Components%20Transfusion.pdf
**BLOOD: GENERAL ALGORITHM FOR APPROPRIATE UTILIZATION**

<table>
<thead>
<tr>
<th>Patient with low or declining H/H</th>
<th>Rule-out other causes of instability (e.g., septic or cardiogenic shock, unstable arrhythmia)</th>
<th>Give PRBCs as needed based upon estimated blood loss and degree of hemodynamic instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamically and/or neurologically unstable, signs of tissue hypoperfusion, or overt bleeding?</td>
<td>Obtain surgical/IR consultation for situations involving overt bleeding or other surgical indications</td>
<td>Give FFP 15-20 ml/kg (1 unit ~ 300 ml) if INR &gt; 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Give cryoprecipitate 20 units if fibrinogen &lt; 110 mg/dl</td>
</tr>
<tr>
<td></td>
<td>For coagulopathies related to warfarin, new oral-anticoagulants (e.g. dabigatran), and antiplatelet agents, discontinue drug. See below for additional information. Consider hematology consult for complex coagulopathies</td>
<td>Give one apheresis platelet unit if platelet count &lt; 50 thous./mcl</td>
</tr>
<tr>
<td>Hgb &lt; 7.0 (or ≥ 7.0 in ACS patient)?</td>
<td>May give PRBC after consideration of risks and benefits</td>
<td>Do not transfuse blood</td>
</tr>
<tr>
<td></td>
<td>Early consideration for obtaining iron panel, folate, B12 levels and treating deficiencies; rule-out potential hemodilution-mediated Hb decline; reduce iatrogenic anemia; consider hematology consultation</td>
<td></td>
</tr>
</tbody>
</table>

Considerations anticoagulant reversal: Heparin effect may be suggested by isolated prolongation of the PT, whereas LMWH frequently will not prolong standard tests of coagulation. For both agents the proper reversal agent is Protamine Sulfate. There is no role for plasma in the reversal of UFH or LMWH effect; LMWH effect is only partially reversed by Protamine. Direct Thrombin Inhibitors (Argatroban, Pradaxa) typically cause prolongation of all routine coagulation studies and may cause spuriously low fibrinogen levels. Thrombin time can be used to estimate (qualitatively) presence of residual effect. Current reversal strategies for Anti-Xa (Rivaroxaban and Apixaban) and Direct Thrombin Inhibitors include cessation of the anticoagulant, applying direct pressure for compressible sites of bleeding, surgical attention where indicated, and, possibly, administration of PCCs and rVIIa. Options for warfarin reversal in patients with major bleeding events include Vitamin K, FFP, PCC and rVIIa. Exercise caution when dosing hemostatic agents since these agents may provoke thrombotic complications in some patients.
References

1. Segal JB, Dzik WH on behalf of the Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion 2005; 45:1413-1425


