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An assessment of blood transfusion practice guidelines: What quality of indication is being employed to grow transfusion guideline endorsements?

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Abstract: Transfusion of blood components is widely utilized in the management of medical and surgical conditions. Though transfusion is a life-saving intervention, there has been debate about the standardization of blood transfusion practices. There has been a tremendous response in literature generated from multiple medical specialties regarding appropriate use of blood products to guide clinicians in their transfusion decisions. However, the consequence of numerous guidelines from multiple specialties results in varying recommendations for transfusion practices. This study was designed to compare and analyze current guidelines to determine if the recommendations generated to guide clinicians in transfusion decisions are truly supported by quality evidence. We performed a literature search on clinical transfusion practice guidelines from January 2005 to October 2015 with the following computer databases: PubMed/Medline, Cochrane Central, Scopus and the National Guideline Clearinghouse. Additional websites and publications, such as the Australian and New Zealand Society of Blood Transfusion, were also searched for guidelines missed from the computer database search. Key words that were used for the search include the combination of the following keywords: blood, blood component, blood product, transfusion, guidelines. The resulting eleven guidelines were analyzed for the following areas: characteristics and composition of the guideline working group panel, literature and evidence utilized for the systematic review, databases utilized to retrieve evidence and literature for the systematic review, methodologies employed by guideline committees to grade strength and quality of evidence and recommendations, quantity of recommendations suggested, and specific transfusion thresholds and/or clinical settings for transfusion of blood products. We developed a three-tiered classification system in order to compare the level of evidence and strength of recommendations generated by each guideline even with the utilization of seven difference grading systems. A total of 107 recommendations were generated about packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate transfusion. Of the 107 recommendations, 48 (48.86%) of the recommendations were specific to the use of packed red blood cells, 31 (28.97%) of the recommendations were specific to the use of fresh frozen plasma, 15 (12.02%) of the recommendations were specific for the use of platelets, and only 13 (12.15% recommendations were specific to the use of cryoprecipitate. Future research should thus be stimulated and directed at providing more abundant and high quality evidence regarding the use and safety of blood components in the perioperative setting.

Keywords: Health and environmental sciences; Biopractice guideline; Blood components; Blood platelets; Blood transfusions; Evidence-based medicine

Background

Transfusion of blood components is widely utilized in the management of medical and surgical conditions. With the discovery of blood types and advancements in medicine, transfusion can be a life-saving intervention. One of the most important reasons for red blood cell (RBC) transfusion is to restore, or maintain, oxygen delivery to vital organs in the human body. Fresh frozen plasma (FFP) transfusion is utilized to treat coagulopathies, life threatening bleeding diathesis and reverse effects of warfarin. Cryoprecipitate is indicated for the treatment of von Willebrand's disease, Hemophilia A, Factor XIII deficiency and hypofibrinogenemia, especially when recombinant products are not available. In 2003, the National Blood Data Resource Center estimated that 14 million units of whole blood were collected, processed into 27 million units of blood products and subsequently transfused in to 4.5 million medical and surgical patients.[1] though transfusion is a life-saving intervention, there is continuing debate about the standardization of blood transfusion practices. Not only has blood become a scarce resource in a large growing population, but transfusion of blood and blood products also carry significant risks.

Oxygen is carried in red blood cells and reversibly bound to the tetramer hemoglobin. Adequate oxygenation of the tissues is dependent on the balance of oxygen consumption and oxygen delivery. Oxygen consumption can remain constant over a wide range of oxygen delivery. However as oxygen delivery reaches a critical threshold, tissue extraction of oxygen cannot be further increased to meet the metabolic needs of the tissue. Oxygen delivery below the critical threshold results in the beginning of anaerobic metabolism and the production of substrates such as lactate, nicotinamide adenine dinucleotide (NADH), and reduced cytochrome oxidase. This critical threshold of

oxygen delivery occurs at different levels in different organ systems. The critical threshold is dependent on the regional and global blood flow regulation, as well as the metabolic needs of the organs.

Oxygen delivery (DO_2) to the whole body is dependent on the relationship between cardiac output (CO) and oxygen content (CaO_2) in the arterial blood [equation 1].

Oxygen consumption (VO_2) in the whole body is dependent on cardiac output and the oxygen content difference between arterial (CaO_2) and venous blood (CvO_2) [equation 2].

$DO_2 = CO \times CaO_2$ (normal range: 460 to 650 $mL/min/m^2$)

[equation 1]

$VO_2 = CO \times (CaO_2 - CvO_2)$ (normal range: 96 to 170 $mL/min/m^2$)

[equation 2]

Where:

$CaO_2 = (Hb \times 1.39 \times SaO_2) + (0.003 \times PaO_2)$

$CvO_2 = (Hb \times 1.39 \times SvO_2) + (0.003 \times PvO_2)$

Hb, hemoglobin; SaO_2, arterial oxygen saturation; PaO_2, arterial oxygen tension; SvO_2 mixed venous oxygen saturation; PvO_2, mixed-venous oxygen tension

Reduction in whole body oxygen delivery can therefore result from either, decrease in cardiac output, or decrease in arterial blood oxygen content (profound anemia, massive hemorrhage, hypoxemia, and decrease in oxygen saturation). In addition to cardiac output and arterial blood oxygen content influencing whole body oxygen delivery, microvascular capillary regulatory mechanisms can also affect tissue oxygen delivery. Functional physiologic shunting can decrease tissue oxygen delivery, while pharmacologic manipulation of microvasculature can increase tissue oxygen delivery.[2]

Theoretically, red blood cell transfusion is capable of enhancing arterial blood oxygen content, and thereby increasing total whole body oxygen delivery. However the use of red blood cell transfusion to manipulate and potentially increase tissue oxygen delivery is complex and its efficacy is not completely clear.[3-7] Transfusion increases hemoglobin levels (hence increase in oxygen content) and in cases where there is a reduction of preload, transfusion can additionally increase cardiac output and thus total body oxygen delivery. However, increasing hemoglobin levels and oxygen content via transfusion may not lead to the immediate desired result of increase oxygen delivery at the tissue level.[8-12] The transfusion of stored red blood cells can trigger biochemical and inflammatory reactions and potentially result in decreased oxygen delivery at the tissue level.[8-12]

Fresh frozen plasma is one of the least understood blood products. It contains albumin, globulins, fibrinogen and other coagulation factors. Even though it has limited recommendations for its use, it is most often used to treat bleeding disorders when a coagulation factor or multiple coagulation factors are deficient or no coagulation factor-specific concentrate is available.[13] Recommended uses for fresh frozen plasma are listed in table 1. Fresh frozen plasma is the most frequently misused blood product.[14,15]

Table 1. Recommended uses for FFP

Single coagulation factor deficiencies
Multiple coagulation factor deficiencies with severe bleeding in disseminated intravascular coagulation (DIC)
Thrombotic thrombocytopenic purpura (TTP)
Reversal of warfarin effect
Surgical bleeding and hemostasis
Hemorrhagic disease of the newborn
Neonates with coagulopathy and in need for a surgical procedureRed cell T antigen in newborns

Cryoprecipitate is the portion of the plasma that is rich in coagulation factors, including factor VIII, fibrinogen, von Willebrand factor and factor XIII.[13] Cryoprecipiate is used primarily for the reversal of hypofibrinogenemia caused by massive transfusion or disseminated intravascular coagulation (DIC). It is also considered for use in treatment of von Willenbrand's disease, Hemophila A, and Factor XIII deficiency when recombinant products are not available.

Platelets are administered to treat either thrombocytopenia or provide functional platelets. Thrombocytopenia, a decrease in number of circulating platelets, is caused by either an increased destruction (idiopathic,

immunologically-mediated, DIC) or decreased production of platelets (myelosuppressive drugs, radiation, chronic alcohol use).

Blood component therapy can be potentially life-saving and at the same time can have deleterious effects. Thus transfusion of blood products should not be taken lightly. Ideally blood product should only be transfused when necessary. If clinicians could easily monitor for optimal oxygen delivery and coagulation status, blood product transfusions could be optimized. However, in rapidly changing clinical situations, it is challenging to predict the need for blood products precisely. With this in mind, transfusion triggers or thresholds based on measurable physiological parameters, could aid and guide clinicians in making the decision for transfusion therapy. It is expected that these transfusion thresholds are developed from quality evidence and based on rigorous clinical trials and studies that demonstrate improvement in patient outcomes.

History of Perioperative Transfusion

There is significant variability in transfusion practices among the different medical specialties. Historically, a hemoglobin of 10 g/dL and a hemotocrit of 30% were widely used and accepted as "transfusion triggers" for red blood cell transfusion particularly in the surgical setting.[16] In the 1970s, red blood cells were often times withheld until symptoms of anemia developed or there was a clinically significant drop of <10 g/dL in hemoglobin.[17-19] In 1988 the National Heart, Lung and Blood institute, the Office of Medical Applications of Research, the Warren Grant Magnuson Clinical Center of the National Institute of Health, and the Food and Drug Administration convened the Consensus Development Conference on Perioperative Red Cell Transfusion to discuss the criteria for perioperative red blood cell transfusion, the morbidity of anemia in the perioperative period, and immediate and long-term risks of transfusion. This consensus conference concluded that available evidence at the time did not support a single criterion for red blood cell transfusion, mild-moderate anemia did not contribute to perioperative morbidity, and transfusions should be kept to a minimum due to the documented risks of infection and deleterious immune modulation.[20] The consensus conference concluded that future research was necessary to define the best indications for perioperative red blood cell transfusion.

Different authors have suggested a range of hemoglobin levels as criterion for transfusion (6.0-10.0g/dL), depending on the presence of several co-morbidities.[21-23] In 1999, the Canadian Critical Care Trials Group demonstrated that a restrictive strategy of red blood cell transfusion in 838 critically ill patients reduced hospitalization mortality rates in a multicenter, randomized controlled clinical trial referred to as the Transfusion Requirements in Critical Care (TRICC) trial.[24] Except in patients with acute myocardial infarction and unstable angina, a restrictive transfusion strategy (threshold of hemoglobin 7.0g/dL; hemoglobin range of 7.0-9.0g/dL) was as effective, if not significantly better at lowering hospital mortality rates, than a liberal transfusion strategy (hemoglobin threshold of 10.0g/dL; hemoglobin range of 10.0-12.0g/dL).

In 2001, a randomized controlled clinical trial was performed to determine if a low transfusion threshold was safe in critically ill patients with known cardiovascular disease.[25] This study concluded that there was no difference in mortality or myocardial infarction rates in the restrictive (transfusion threshold of hemoglobin 7.0g/dL; hemoglobin range 7.0 - 9.0g/dL) versus liberal (transfusion threshold of haemoglobin 10.0g/dL; hemoglobin range 10.0 - 12.0g/dL) transfusion groups.[25] However, it suggested that a restrictive transfusion strategy appeared to be safe in most patients with cardiovascular disease, with the exception of patients with acute myocardial infarcts and unstable angina. On the contrary, in other studies, in patients undergoing coronary artery bypass graft surgery or myocardial revascularization there was no difference in mortality rates when a restrictive (hemoglobin 8.0g/dL) transfusion
threshold was compared to a liberal (9.0g/dL) transfusion threshold.[26,27]

In contrast to packed red blood cells, there is little data on the relationship of transfusion of coagulation blood products, such as platelets, fresh frozen plasma, cryoprecipitate, and patient outcomes. Of the coagulation blood products mentioned, there are more data about the transfusion of platelets in the perioperative period. In 2004, a study with 1,720 patients who received platelet transfusion, suggested a significant association between platelet transfusion and the risk of infection, stroke and

death.[28] There have been no prospective randomized trials to date investigating the liberal or prophylactic use of platelet transfusion and its

association with increased rate of stroke and death. Moreover, there is limited data from randomized controlled trials regarding the threshold for transfusion of fresh frozen plasma and cryoprecipitate, and patient outcomes.

Risks of Blood Product Transfusion

More than twenty years ago, blood and blood component transfusion were thought to be relatively safe. Then in the 1980s, up to 1 in 100 blood units was found to transmit the human immunodeficiency virus (HIV) or hepatitis C virus (HCV), as plasma did not undergo viral inactivation.[29] There have been significant advancements in transfusion medicine in the past 30 years, such as nucleic-acid testing, that have reduced the estimated residual risk of infection with the HIV or HCV to 1 in 1.5 million to 1 in 2 million units transfused.[30] Current risk of transmission of blood-borne viruses are listed in table 2.[31]

Table 2. Contemporary risk of transmitting any of the blood-borne viruses.[31]

Virus	Risk per Unit Transfusion	Transmission Rate	Window Period
Human Immunodeficiency Virus 1&2	1:2,135,000	90%	11 days
Hepatitis C Virus	1:1,935,000	90%	10 days
Hepatitis B Virus	1:205,000	70%	59 days
Human T-lymphotrophic Virus	1:3,000,000	30%	51 days
West Nile Virus	1:10,000 to 1,000*	unknown	-
Parvovirus B19	1:40,000 to 3,000	low	-
Hepatitis A/E	1:1,000,000	low	-

*prior to nucleic acid testing

Emerging infections, defined as those infections whose incidence in humans has increased within the past two decades or threatens to increase in the near future, may have an asymptomatic blood-borne phase and may exist and can be transmittable by transfusion. Current infectious agents that are emerging to threaten blood and blood component safety include, but are not limited to, are: human variant Creuztfeld-Jakob disease, West Nile virus, *Babesia* species, GB virus C-hepatitis G virus, SEN virus, TT virus, human herpesvirus 8, and simian foamy virus.[32-34]

Though transmission of infection by blood transfusion has decreased significantly, transfusion-related acute lung injury (TRALI) has now become the leading cause of transfusion related mortality. Fresh frozen plasma administration has been shown to be an independent risk factor for TRALI in trauma, medical and surgical ICU patient.[35] Intensive care unit patients, enrolled in the 2004 CRIT (Anemia and Blood Transfusion in CRITical Care) study, who received red blood cell transfusions, experienced a higher incidence of overall complications. The study demonstrated that the number of red blood cell transfusions a patient received was independently associated with a longer ICU stay, length of hospital stay, and increase in mortality.[36] With these current transfusion risks in mind, practitioners are relying heavily on transfusion practice guidelines and recommendations. The goal of these clinical transfusion practice guidelines and recommendations is to limit unnecessary transfusion of blood products, improve blood component transfusion therapy for patients and hopefully improve clinical outcomes.

History of the Development of Transfusion Guidelines

The development of guidelines were proposed in 1990 by the Institute of Medicine to reduce inappropriate health care variation by aiding physician decision- making.[37] Decision-making in healthcare should acknowledge benefits and risks

of medical interventions, as well as the underlying quality of evidence to support such interventions.

The number of practice guidelines has mushroomed significantly, with each of the medical societies developing their own set of guidelines for areas of interest for them. [38] A variety of medical specialties have published recommendations, on the use of blood products, to guide clinicians in their transfusion decisions. In the 1980s, the National Institute of Medicine held consensus conferences on the use of red blood cells, fresh frozen plasma, and platelets.[39-41] In the 1990s, the American College of Physicians and American College of Pathologists issued guidelines regarding red blood cell and fresh frozen plasma, cryoprecipitate and platelet transfusion respectively.[42,43] The American Association of Blood Banks also generated guidelines regarding transfusion during coronary artery bypass graft surgery and appropriate blood utilization.[44,45] In the same decade, the American Society of Anesthesiologists (ASA) developed a Task Force to develop guidelines regarding blood component therapy.[46] However, the consequence of numerous guidelines from multiple specialties results in varying recommendations for each intervention, which can be confusing for physicians. Furthermore, when several physicians are involved in the care of a patient, their decisions when to transfuse can differ significantly, based on what guideline the care-giver is following.

Guidelines for physicians should comprise of the following: the scope of the practice guidelines, current interventions and practices considered, strength of recommendations and the quality of used evidence. The recommendations developed in guidelines ideally should be based on strong evidence. However in actuality, guidelines may generate strong recommendations on consensus expert opinions rather than on high quality evidence.[37] In addition, these guidelines use multiple systems to grade the quality of evidence, as well as to classify the strength of their recommendations. Thus, it is important to compare and analyze current guidelines, to determine variations in recommendations and if the recommendations generated to guide clinicians are truly supported by quality evidence. In addition, it is also important to consider and evaluate guidelines for the composition of their working group, types of studies used to develop guidelines, and the specific methodologies utilized to grade evidence and classify recommendations. In this study, we compared different guidelines for variations in guideline development, recommendations and their level of evidence.

Methods

A comprehensive literature search on clinical transfusion guidelines of blood components was identified and performed using the following computer databases: PubMed/Medline, Cochrane Central, Scopus and the National Guideline Clearinghouse. Additional websites and publications of relevant scientific societies, such as the Australian and New Zealand Society of Blood Transfusion, were also searched for guidelines missed from the computer database search. Key words that were used for searching the databases include the combination of the following keywords: blood, blood component, blood product, transfusion, guidelines. Of those database searches of articles, only articles from January 2005 to October 2015 written in the English language were retrieved. The articles/guidelines were limited to the last 5 years as we assumed that the literature within that time frame was most current and clinically relevant. However some guidelines outside of this time period were included, in order to provide complete representation of guideline recommendations from countries not represented in the initial computer database searches. In these cases, only the most current practice guideline published from the societies were utilized. Relevance of the articles to be retrieved was evaluated and included if there were clear transfusion indications and recommendations stated within the article. Articles regarding transfusion practices in children or neonates were not included in this study. A total of eleven international guidelines were included in this study for final analysis ranging from the year 2001 to 2015.

The resulting eleven guidelines were analyzed for the following areas: characteristics and composition of the guideline working group panel, literature and evidence utilized for the systematic review, databases utilized to retrieve evidence and literature for the systematic review, methodologies employed by guideline committees to grade strength and quality of evidence and recommendations, quantity of recommendations suggested, and specific transfusion thresholds and/or clinical settings for transfusion of blood products.

The eleven guidelines use seven different systems to grade the strength of recommendations and the level of evidence. In order to help us compare the level of evidence and strength of recommendations amongst these guidelines, we

developed a three-tiered classification system for both grading level of evidence and strength of recommendation (Table 2 and 3). This system was applied to all eleven guidelines reviewed. The terms "strong," "intermediate," and "low" level of evidence as used in this study are described and defined in table 3. The terms "strong," "intermediate," and "low" grade of recommendation as used in this study are described and defined table 4.

Table 3. Compilation of Level of Evidence Grading

Grading of Evidence	GRADE	AHRQ	USPSTF (After May 2007)	USPSTF (Before May 2007)	AHA/ACC	NHMRC	ASA
STRONG	High/A	1A 1B	High (Class I)	Good	A	I II	Support
INTERMEDIATE	Moderate/B	2A 2B	Moderate (Class II)	Fair	B	III1 III2	Suggest
LOW	Low /C Very Low /D	3 4	Low (Class III)	Poor	C	III3 IV	Equivocal Silent Insufficient Inadequate

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation
USPSTF = U.S. Preventative Task Force
ACC/AHA = American College of Cardiology/American Heart Association
ASA = American Society of Anesthesiologists
NHMRC = Australian National Health and Medical Research Council
ARHQ = Agency for Healthcare Research and Quality

Table 4. Compilation Strength of Recommendation Classification

Strength of Recommendation	GRADE	AHRQ	USPSTF (After May 2007)	USPSTF (Before May 2007)	AHA/ACC	NHMRC	ASA
STRONG	Strong (1)		A (Level 1)	A B	Class I	A	Strongly agree Agree
INTERMEDIATE			B (Level 2) C	C	Class IIa Class IIb	B	Equivocal
WEAK	Weak (2)		D (Level 3) I	D I	Class III	C D	Disagree Strongly disagree

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation

USPSTF = U.S. Preventative Task Force
ACC/AHA = American College of Cardiology/American Heart Association
ASA = American Society of Anesthesiologists
NHMRC = Australian National Health and Medical Research Council
ARHQ = Agency for Healthcare Research and Quality

Results

The bibliographic search conducted was limited to articles written in the English language published during the period from January 2005 to October 2015. A comprehensive literature search to identify guidelines relevant to transfusion of blood components was performed and yielded the following results: PubMed/Medline (701), Cochrane Central (38), Scopus (4,292), and the National Guidelines Clearinghouse (2,073). Additional publications from relevant scientific societies, such as the Australian and New Zealand Society of Blood Transfusion, were also searched to identify guidelines missed from the database screen. An initial screening of these references identified potentially relevant articles. The final analysis of these articles resulted in the identification of 11 international guidelines addressing clinical transfusion practices of blood components.

Guidelines Working Group Panel Composition

Table 5 and figure 1 report the panel composition of working groups for each of the eleven guidelines. To address the composition of working groups that prepared guidelines we looked at the number of total members, medical specialties represented, international/national societies represented, and consulting methodologists involved in the working group panels. Six of eleven guidelines reported the number of medical specialties represented by each panel member. However, only five guidelines detailed the number of international/national medical societies represented by each panel member. Similarly, five of eleven guidelines reported the total number of members composed their working group. Only two of eleven guidelines reported involving consultant methodologists in the working group panel.

Table 5. Working Group Panel Composition

Author	Number of members	Number of specialties represented	Number of societies represented	Number of consulting methodologists
Roback et al (2010)	17	6 (9 members)	6	3
Napolitano et al (2009)	NM	5	2	NM
Dellinger et al (2008)	55	NM	16	NM
Ferraris et al (2007)	17	NM	NM	NM
Spahn et al (2007)	NM	5	5	NM
Stainsby et al (2006)	100	NM	3	NM
Wong et al (2007)	NM	2	NM	NM
Droubatchevskaia et al (2007)	NM	3	NM	NM

Author	Number of members	Number of specialties represented	Number of societies represented	Number of consulting methodologists
ASA Task Force (2006)	10	4	NM	2
New Zealand (2001)	NM	3	NM	NM
Cochrane (2009)	NM	NM	NM	NM

("NM " indicates not mentioned)

Figure 1. Number of Members in Working Group Panel

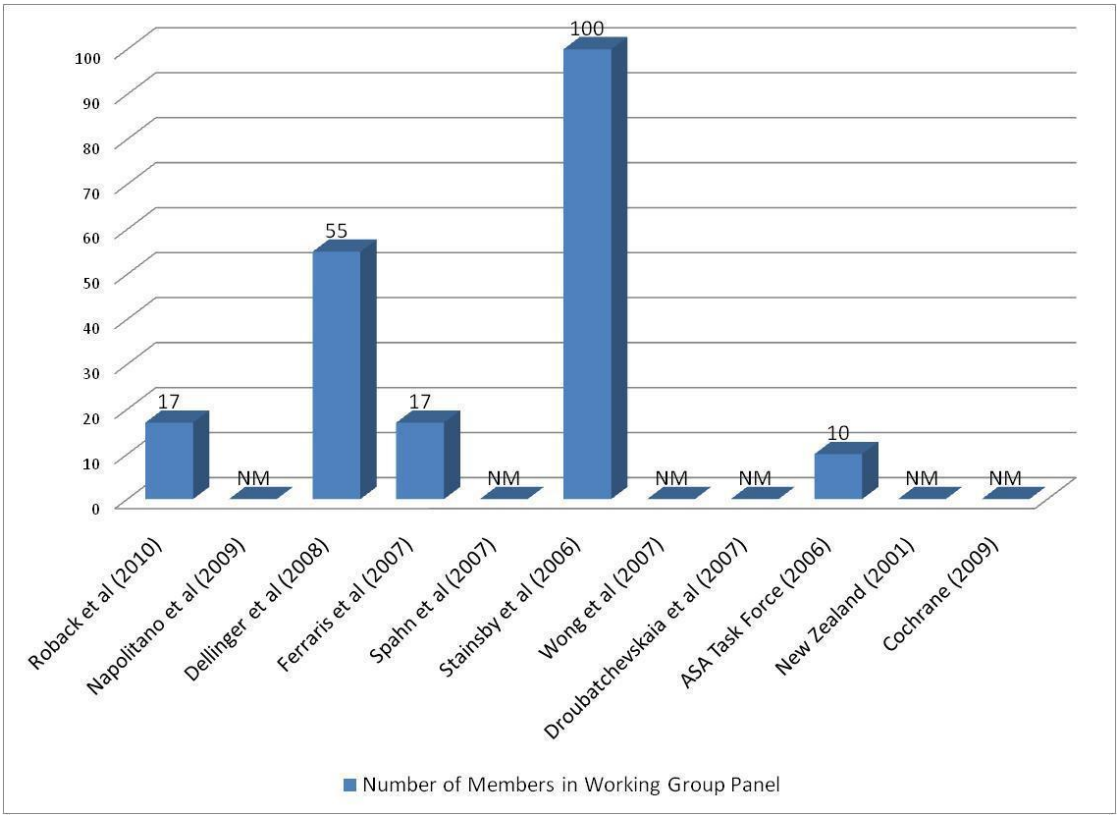


Table 6 and figure 2 report the number of medical specialties represented in each working group panel for the eleven guidelines. Six of the eleven guidelines reported having a panel member specialized in internal medicine and/or critical care medicine. Five of the eleven guidelines reported having a panel member specialized in hematology, anesthesiology, or surgery. Within the guidelines mentioning a panel member specializing in surgery, three specified having a member from trauma and/or thoracic surgery. Three of the eleven guidelines also reported having a panel member specialized in pathology. Pediatrics, obstetrics, transfusion pathology, oncology, transfusion medicine were mentioned to be represented in only one of the guidelines.

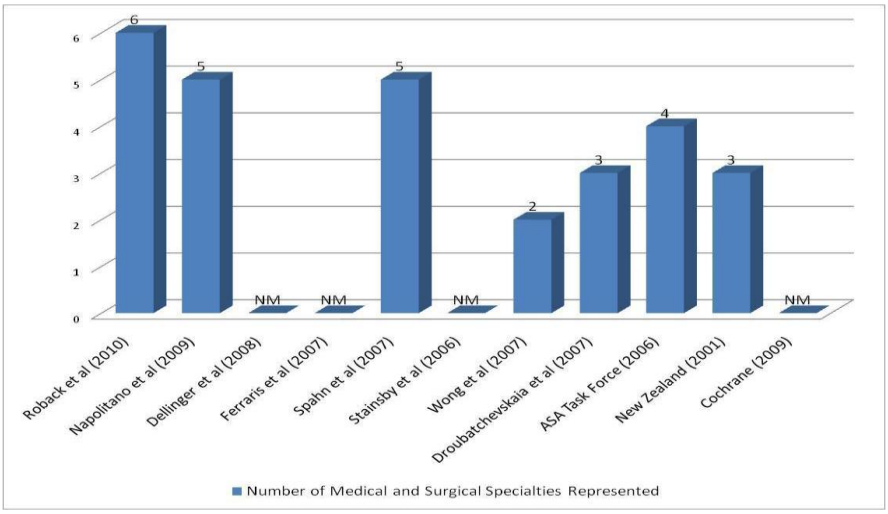
One of eleven guidelines reported five medical specialties represented, three of eleven guidelines reported four medical specialties represented, one of eleven guidelines reported three medical specialties represented, two of eleven guidelines

reported two medical specialties represented, and two of eleven guidelines reported only one medical specialty represented in the working group panel. Emergency medicine, pediatrics and obstetrics specialties were reported in the working group panel of only one guideline. Orthopedic surgery, vascular surgery, oncologic surgery, solid organ transplant surgery and neurosurgery were not represented (or mentioned) in any of the eleven guidelines.

Table 6. Medical Specialties Represented in Working Group Panel

Author	Hematology	Pathology	Anesthesiology	Internal Medicine/ Critical Care	Emergency Medicine	Pediatrics	Surgery (Thoracic/ Trauma)	Obstetrics	Total Number of Specialties
Roback et al (2010)	X (9)	X (9)	X(2)	X (4)	NM	X(2)	NM	NM	5
Napolitano et al (2009)	NM	NM	NM	X (?)	NM	NM	X (?/Trauma)	NM	2
Dellinger et al (2008)	NM	NM	NM	X (?)	NM	NM	NM	NM	1
Ferraris et al (2007)	NM	NM	X	NM	NM	NM	X (Thoracic)	NM	2
Spahn et al (2007)	X	NM	NM	X	X	NM	X (?/Trauma)	NM	4
Stainsby et al (2006)	X	NM	NM	NM	NM	NM	NM	NM	1
Wong et al (2007)	X	X	X	X (Transfusion)	NM	NM	NM	NM	3
Droubhatchevskaia et al (2007)	X	X	NM	X	NM	NM	NM	NM	3
ASA Task Force (2006)	NM	X (Transfusion)	X	NM	NM	NM	X	X	4
New Zealand (2001)	X	NM	X	X (Oncology)	NM	NM	X	NM	4
Cochrane (2009)	NM	NM	NM	NM	NM	NM	NM	NM	NM

Figure 2. Number of Medical and Surgical Specialties Represented



Evidence and Systematic Reviews Utilized to Generate Guidelines

Table 7 demonstrates the study design of the evidence utilized in the development of the eleven guidelines. Four of the eleven guidelines reviewed listed detailed methods of their literature review and their study design of the literature searched and reviewed. One guideline only mentioned the study designs they excluded from their literature search. Five of eleven guidelines analyzed in this study did not reveal the study designs of the literature they utilized in their search and in the development of their guidelines.

Table 7. Systematic review: Study Design of Evidence Utilized

Author	Randomized Controlled Trials	Case Control	Case Reports	Observational	Systematic Reviews	Meta-analysis	Guidelines	Abstracts	Editorials
Roback et al (2010)	X			X					
Napolitano et al (2010)			excluded		excluded				Excluded
Dellinger et al (2008)	NM								
Ferraris et al (2007)	X		X	X					
Spahn et al (2007)	X	X	X	X	X		X	X	
Stainsby et al (2006)	NM								
Wong et al (2007)	NM								
Droubatchevskaia et al (2007)	NM								
ASA Task Force (2006)	NM								
New Zealand (2001)					X	X			
Cochrane (2009)	NM								

("NM " indicates not mentioned)

Table 8 demonstrates the databases utilized to yield the literature searches and reviews performed by each working group for the eleven international guidelines. Six of the eleven guidelines utilized Pubmed/Medline searches and four of the eleven guidelines utilized Cochrane Central searches. One guideline utilized EMBASE, one guideline utilized National Library of Medicine, and another guideline utilized Current Contents. Four of the eleven guidelines did not reveal the types of databases utilized when performing their literature searches for their guideline development.

Table 8. Systematic review: Databases Utilized

Author	Medline/PubMed	EMBASE	Cochrane Central	National Library of Medicine	Current Contents
Roback et al (2010)	NM				
Napolitano et al (2010)	X	X	X	X	
Dellinger et al (2008)	X				
Ferraris et al (2007)	NM				
Spahn et al (2007)	X		X		
Stainsby et al (2006)	X		X		
Wong et al (2007)	X				
Droubatchevskaia et al (2007)					
ASA Task Force (2006)	NM				
New Zealand (2001)	NM				
Cochrane (2009)	X		X		X

Methodology Utilized to Grade Evidence

Table 9 reports the methodology utilized by the eleven guideline's working groups to grade and rate evidence. Three of the eleven guidelines either utilized the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, or the Agency for Healthcare Research and Quality (AHRQ) methodology.[47-51] The five guidelines not utilizing the GRADE or AHRQ methodologies, utilized any one of the following: the U.S. Preventative Task Force (USPSTF) methodology, American College of Cardiology/American Heart Association (ACC/AHA) methodology, Australian National Health and Medical Research Council (NHMRC) methodology or the American Society of Anesthesiologists (ASA) methodology.[52-55]

Table 9. Methodology utilized by Guideline Committees to Rate Evidence

Author	GRADE	USPSTF	ACC/AHA	ASA	NHMRC	ARHQ	Cochrane
Roback et al (2010)	X						
Napolitano et al (2010)		X					
Dellinger et al (2008)	X						
Ferraris et al (2007)			X				
Spahn et al (2007)	X						
Stainsby et al (2006)						X	
Wong et al (2007)						X	
Droubatchevskaia et al (2007)						X	
ASA Task Force (2006)				X			
New Zealand (2001)					X		
Cochrane (2009)							X
TOTAL	3	1	1	1	1	3	1

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation USPSTF = U.S. Preventative Task Force

ACC/AHA = American College of Cardiology/American Heart Association ASA = American Society of Anesthesiologists

NHMRC = Australian National Health and Medical Research Council ARHQ = Agency for Healthcare Research and Quality

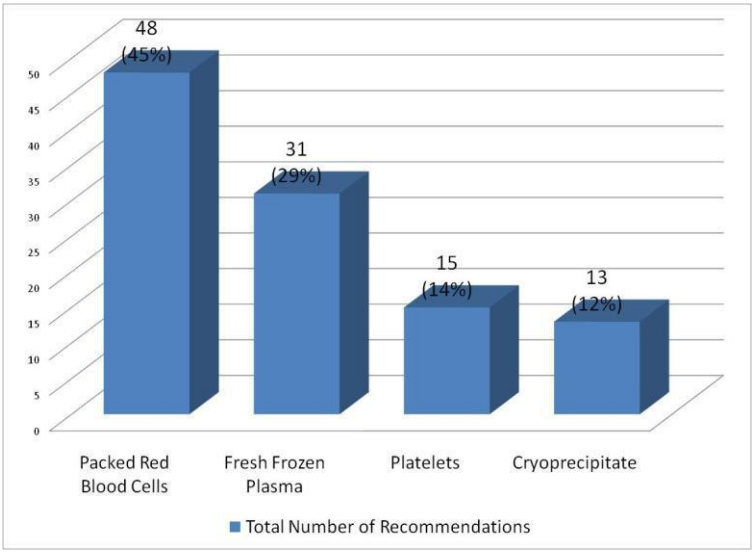
Practice Guideline Recommendations

Table 10 and figure 3 represent the total number of recommendations made by the working group panel regarding use of blood and blood product transfusion in the perioperative setting. The total number of recommendations ranged from one to twenty-eight total recommendations for each of the guidelines. A total of 107 recommendations were generated about packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate transfusion. Of the 107 recommendations, 48 (48.86%) of the recommendations were specific to the use of packed red blood cells, 31 (28.97%) of the recommendations were specific to the use of fresh frozen plasma, 15 (12.02%) of the recommendations were specific for the use of platelets, and only 13 (12.15%) recommendations were specific to the use of cryoprecipitate. (Figure 3)

Table 10. Number of Recommendations Suggested for each Component of Blood Therapy

Author	Packed Red Blood Cells	Fresh Frozen Plasma	Platelets	Cryoprecipitate	Total Regarding Blood Products
Roback et al (2010)	1	6	0	0	7
Napolitano et al (2010)	28	0	0	0	28
Dellinger et al (2008)	2	1	1	0	4
Ferraris et al (2007)	9	0	0	0	9
Spahn et al (2007)	1	1	3	1	6
British Columbia (2006/2007)	1	11	7	2	21
ASA Task Force (2006)	2	5	3	3	8
New Zealand (2001)	3	7	6	2	14
Cochrane (2009)	1	0	0	0	1
TOTAL	48/107 (48.86%)	31/107 (28.97%)	15/107 (12.02%)	13/107 (12.15%)	107/107 (100%)

Figure 3. Total Number of Recommendations

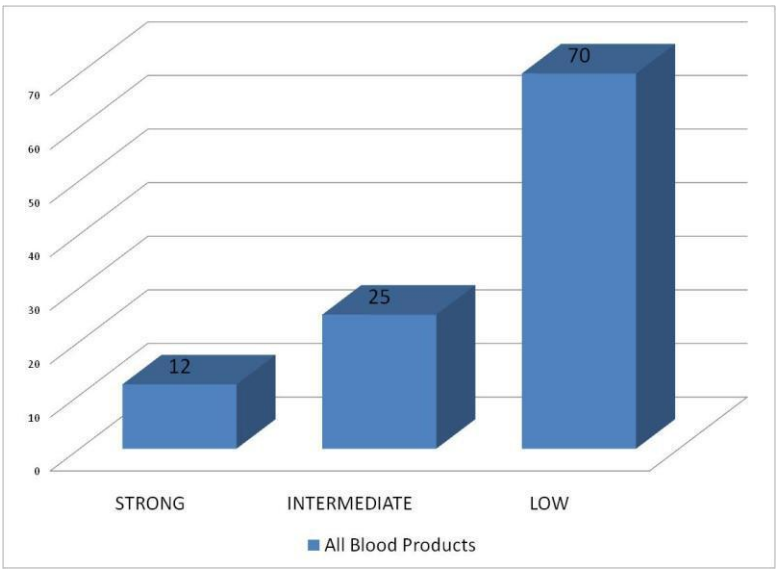


Of the 107 recommendations, table 11 and figure 4 demonstrate that only 12 (11.21%) recommendations were generated from "strong" level evidence, 25 (23.36%) recommendations were generated from "intermediate" level evidence, and 70 (65.42%) recommendations were generated from "low" level evidence.

Table 11. Level of Evidence Utilized for All Blood Product Recommendations

Level of Evidence	Packed Red Blood Cells	Fresh Frozen Plasma	Cryoprecipitate	Platelets	Number/Total (%)
STRONG	4 (8.33%)	7 (22.58%)	0 (0.00%)	1 (6.67%)	12/107 (11.21%)
INTERMEDIATE	24 (50.00%)	1 (3.23%)	0 (0.00%)	0 (0.00%)	25/107 (23.36%)
LOW	20 (41.67%)	23 (74.19%)	13 (100%)	14 (93.33%)	70/107 (65.42%)
Total	48	31	13	15	107/107 (100%)

Figure 4. Level of Evidence Utilized for All Blood Product Recommendations

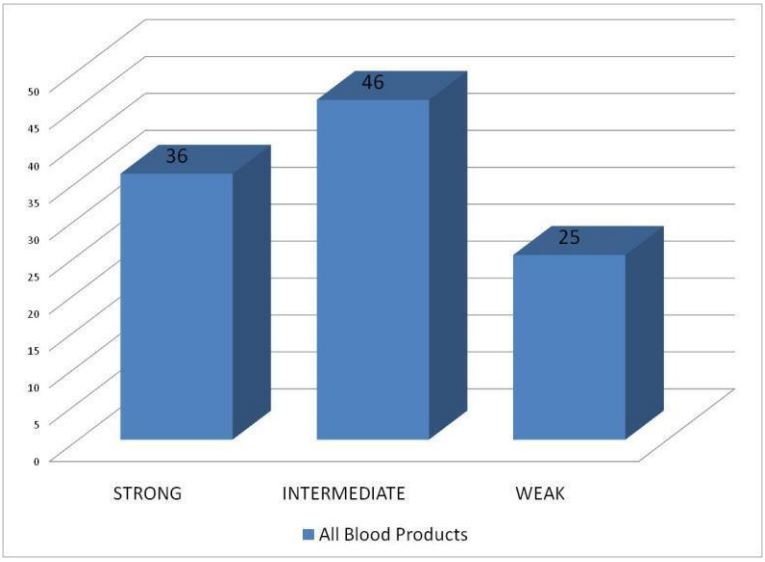


Of the 107 recommendations, table 12 and figure 5 demonstrate that 36 (33.64%) recommendations were classified as a "strong" recommendation to perform the intervention, 46 (42.99%) recommendations were classified as an "intermediate" recommendation to perform the intervention, and 25 (23.36%) recommendations were classified as a "weak" recommendation to perform the intervention.

Table 12. Strength of Recommendations for All Blood Products

Strength of Recommendation	Packed Red Blood Cells	Fresh Frozen Plasma	Cryoprecipitate	Platelets	Number/Total (%)
STRONG	10 (20.83%)	9 (29.03%)	7 (53.85%)	10 (66.67%)	36/107 (33.64%)
INTERMEDIATE	31 (64.58%)	10 (32.26%)	5 (38.46%)	0 (0.00%)	46/107 (42.99%)
WEAK	7 (14.58%)	12 (38.71%)	1 (7.69%)	5 (33.33%)	25/107 (23.36%)
Total	48	31	13	15	107/107 (100%)

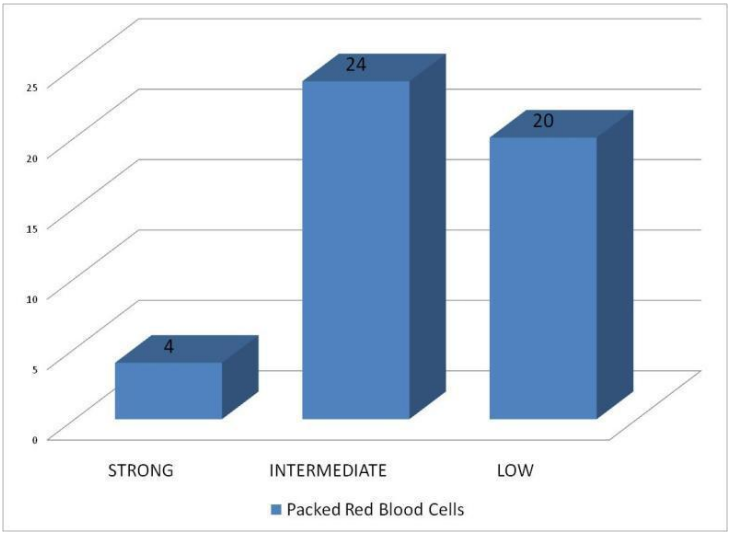
Figure 5. Strength of Recommendations for All Blood Products



Recommendations Regarding Clinical Use of Red Blood Cells

Table 10 demonstrates that a total of 48 of the 107 recommendations were relevant to packed red blood cell use. Of the 48 recommendations, table 11 and figure 6 demonstrate that 4 (8.33%) recommendations were generated from "strong" level of evidence, 24 (50.00%) recommendations were generated by "intermediate" level evidence, and 20 (41.67%) recommendations were generated by "low" level evidence.

Figure 6. Level of Evidence Utilized for Packed Red Blood Cell Recommendations



Of the 48 recommendations, table 12 and figure 7 demonstrate that 10 (20.83%) recommendations were classified as a "strong" recommendation to perform the intervention, 31 (64.58%) recommendations were classified as an "intermediate" recommendation to perform the intervention, and 7 (14.58%) recommendations were classified as a "weak" recommendation to perform the intervention. Of the 10 "strong" recommendations, 1 (10.00%) recommendation was based on "strong" level of evidence, 3 (30.00%) recommendations based on "intermediate" level of evidence, and 6 (60.00%) recommendations based on "low" level of evidence (Figure 8).

Figure 7. Strength of Recommendations for Packed Red Blood Cells

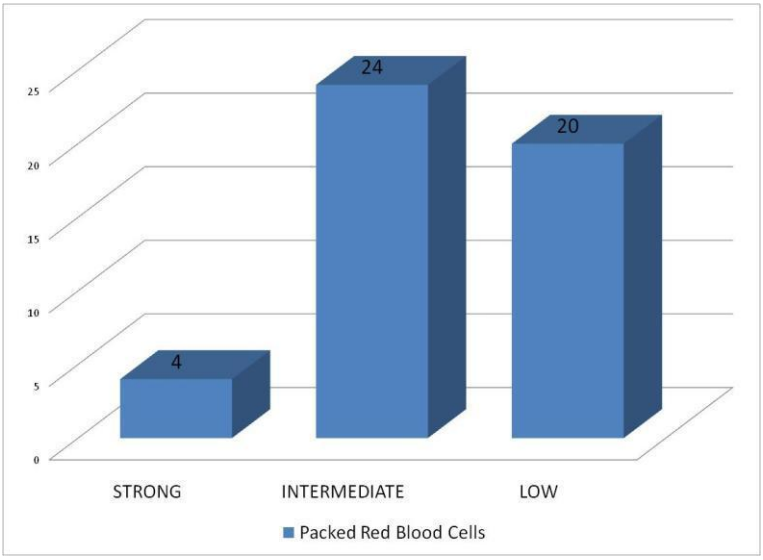
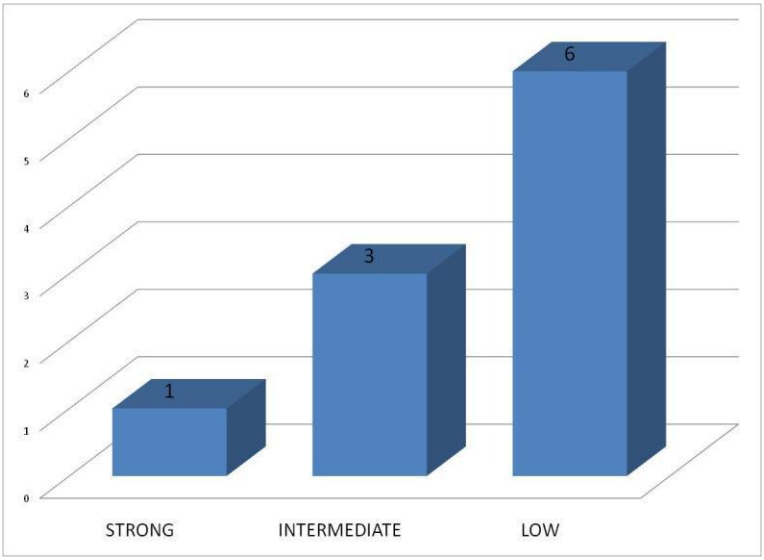


Figure 8. Level of Evidence for "Strong" Recommendations regarding use of RBC



Appendix table 1 summarizes the eleven international guideline recommendations for the clinical use of packed red blood cells. Of the guidelines reviewed, 7 of 10 international guidelines have commented on the indications and utilization of packed red blood cells. A target Hb level of 7-9g/dL is recommended (Dellinger, Level 1B; Spahn, Grace 1C) [51,56], but other target ranges such as Hb 6-10g/dL (ASA, strongly) or 7-10g/dL (Australia, Level IV) has also been recommended as well.
51,54-56

Five guidelines stated RBC should be administered when the hemoglobin level is <7g/dL (Table 13). Napolitano et al recommended **consideration** of transfusion with a Hb <7g/dL in critically ill patients with acute hemorrhage, with hemodynamic instability, with inadequate oxygen delivery (Level 1), requiring mechanical ventilation or resuscitated critically ill trauma and stable cardiac patients without acute myocardial ischemia (Level 2), and Ferraris et al stated it was **reasonable for** transfusion with a Hb <7g/dL in

most post-operative patients (Class 2A, C), and **not unreasonable** for patients on cardiopulmonary bypass with risk for critical end-organ ischemia/injury (Class 2B, C).

[52,53] Dellinger et al strongly recommended the threshold for giving RBC be Hb<7g/dL with a target hemoglobin of 7-9g/dL in adults. They also suggested that a higher hemoglobin level may be required in the setting of myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis in patients (Level 1B, Strong). [56]

Table 13. Guidelines recommending transfusion threshold of Hb <7 g/dL

Organization	Recommendation	Evidence
Napolitano (USPTF)	Level 1 (convincingly justifiable based on scientific evidence) Level 2 (reasonable scientific evidence and strong expert opinion)	Class 1, Class 2 (Prospective RCT, strong prospective and retrospective analysis) Class 2, Class 3 (Strong prospective and retrospective analysis, retrospective data collection)
Dellinger (GRADE)	Strong / Grade 1 (Recommend; benefits do or do not outweigh harm and burden)	Class B (Moderate; RCT with important limitations or very strong evidence from observational studies or case series)
Ferraris (ACC/AHA)	Class 2B (Usefulness/efficacy is less well established by evidence/opinion)	Level C (Consensus opinions of experts)
New Zealand (NHMRC)	-	Level IV (Evidence obtained from case series, either post-test or pretest and post-test)

In Table 14 Napolitano et al suggested that a transfusion threshold of Hb </= 8g/dL may be **beneficial** in patients with acute coronary syndromes who are anaemic on hospital admissions (Level 3).[52] More "restrictive" hemoglobin transfusion triggers were recommended by several guidelines.

Table 14. Guidelines recommending transfusion threshold of Hb </= 8g/dL

Organization	Recommendation	Evidence
Napolitano (USPTF)	Level 3 (Supported by data but lacking adequate scientific evidence)	Class 3 (retrospective data collection)
British Columbia (AHCPR)	Grade C (Absence of directly applicable clinical studies of good quality)	Level IV (Evidence from expert committee reports or opinions and/or clinical experiences of respected authorities)

In Table 15 Ferraris et al stated that for hemoglobin levels <6g/dL, transfusion with RBC is **reasonable** and can be life-saving (Class 2A, C), **reasonable** and life-saving for cardiac operations (Class 2A, C), **reasonable** during cardiopulmonary bypass withmoderate hypothermia except in patients at risk for decreased cerebral oxygen delivery, such as those with histories of cardiovascular disease, diabetes mellitus, cerebrovascular disease, and carotid stenosis (Class 2A, C), and additionally the ASA Task Force **strongly** agreed upon in the setting of a young, healthy patient especially when the anemia is acute and without low cardiopulmonary reserve and high oxygen consumption (strongly). [53,54]

Table 15. Guidelines recommending transfusion threshold of Hb <6 g/dL

Organization	Recommendation	Evidence
Ferraris (ACC/AHA)	Class 2A (weight of evidence/opinion is in favor of usefulness/efficacy)	C (consensus opinions of experts)
British Columbia (AHCPR)	Grade C (absence of directly applicable clinical studies of good quality)	Level IV (evidence from expert committee reports or opinions and/or clinical experiences of respected authorities)
ASA	Strongly agree	Insufficient

In Table 16 four guidelines did not support the use of 10g/dL as a hemoglobin transfusion trigger for RBC. Napolitano et al stated there is **no benefit** of a "liberal" transfusion when Hb >10g/dL in critically ill patients on mechanical ventilation, resuscitated critically ill trauma patients, critically ill patients with stable cardiac disease, or in patients with moderate to severe traumatic brain injury (Level 2). [52] The ASA Task Force **strongly** agreed that RBC are usually **unnecessary** when the hemoglobin level is more than 10g/dL (strongly), Stainsby et al stated it was **rarely indicated** when Hb >10g/dL (Level 1), and the Australian guideline stated that it is **likely inappropriate** to transfuse at that hemoglobin level unless there are specific indications (Level I). [47,54,55] However, Ferraris et al stated that it is **not unreasonable** to transfuse red cells in certain patients with clinical non-cardiac end-organ ischemia, such as the central nervous and gastrointestinal system, whose hemoglobin level is as high as 10g/dL (Class 2B, C). [53] However this statement was modified with the disclaimer that such a "liberal transfusion" it is **unlikely** to improve oxygen transport and is **not recommended** for those purposes (Class 2B, C). [53]

Practice Guideline Recommendations

Almost half (48.86%) of the total recommendations reviewed pertain only to the transfusion of packed red blood cells (Table 10 and figure 3). The rest of the recommendations reviewed pertain to coagulation blood components such as fresh frozen plasma (28.97%), platelets (12.02%), and cryoprecipitate (12.15%). This suggests that there is mounting literature regarding the transfusion of packed red blood cells, but substantial evidence is still lacking regarding the appropriate use and safety of fresh frozen plasma, platelets, and cryoprecipitate.

Of the 107 recommendations reviewed, a majority (65.42%) of the recommendations were based from "low" level of evidence. This "low" level of evidence may include case series or reports, expert reports or opinions, and evidence that is limited in power or demonstrates flaws in the study design. Only 12 (11.21%) recommendations are based on "strong" level of evidence, such as meta-analyses and randomized controlled trials. Our analysis suggests the lack of relationship/association between the quality of evidence reviewed and the strength of recommendations generated by the guideline working panels (Table 11, Table 12, Figure 4, Figure 5). Though 82 (76.63%) recommendations are classified as "strong" or "intermediate" recommendations, they are based solely on "low" level of evidence (Table 12, Figure 5).

Recommendations Regarding Clinical Use of Blood Products

A majority (85.41%) of recommendations for packed red blood cells deemed as "strong" and "intermediate" are based almost entirely (91.67%) on "intermediate" and "low" level of evidence. Of the "strong" recommendations regarding the use of packed red blood cells, majority were based on a "low" level of evidence. More than half (61.29%) of recommendations for fresh frozen plasma deemed "strong" and "intermediate" are based exclusively (74.19%) on "low" level of evidence. All recommendations pertaining to cryoprecipitate transfusion are based solely on "low" level of evidence. A majority of "strong" recommendations for platelet transfusion are based almost entirely (93.33%) on "low" level evidence. With the slight exception of packed red blood cells, all guidelines undividedly reported "strong" and/or "intermediate" recommendations to transfuse coagulation products on the basis of "low" level evidence.

In addition, there was multiple hemoglobin level transfusion triggers are reported amongst the eleven guidelines, and even within a guideline. There was clearly a discrepancy between guideline recommendations about transfusing for a

particular hemoglobin level, as well as, a discrepancy between the quality and strength of evidence to support the recommendation. For example in regard to use of 6g/dL of hemoglobin as a packed red blood cell transfusion trigger, the two organizations utilized the same quality of evidence (consensus opinions of experts) yet generated different recommendations. One organization favored the use and efficacy of the intervention, while the other organization gave the intervention its lowest level of recommendation.[53,54]

In addition, one organization reported two different hemoglobin levels as transfusion triggers in the context of different clinical settings.[53] both recommendation statements were based on "consensus opinions of experts." The recommendation to transfuse at hemoglobin < 6g/dL is graded Class 2A supporting the intervention in favor of its usefulness and efficacy, whereas the recommendation to transfuse at haemoglobin 7g/dL is graded Class 2B giving weaker support to the recommendation as the usefulness and efficacy. It is unclear through analysis of these eleven guidelines what specific hemoglobin level should be utilized as the threshold hemoglobin level to trigger transfusion of packed red blood cells. The only consensus is not to transfuse if the Hb is > 10gm/dl.

The recommendations generated for the use of fresh frozen plasma, platelets, and cryoprecipitate are based on even weaker level of evidence compared to the recommendations generated for use of packed red blood cells. The recommendations for coagulation products are insufficient, both in number of total recommendations and in strength of recommendations. Two organizations have stated a definite threshold to transfuse fresh frozen plasma (PT or aPTT is > 1.5 normal). [58,61] However, the data come from the same quality of evidence (case series, observational studies, and consensus opinion of experts). In the eleven guidelines we evaluated, there is no consensus regarding a definite platelet level or a fibrinogen which should trigger transfusion.

Limitations of Study

The following are the limitations of this investigation. Of the guidelines included, only guidelines published in the English language were reviewed, as well as, only guidelines published in the last ten years were reviewed. We have only reviewed guidelines relevant to adult patients. In addition, only two reviewers screened the initial literature searches performed on PubMed/Medline, Scopus, Cochrane Central and the National Guideline Clearinghouse, and determined that the final eleven guidelines to be selected for inclusion in the study.

In order to compare different guidelines we had to develop a uniform scoring system. These definitions were created to readily compare the eleven guidelines that had all used different grading and classification methodology systems. However, this scoring system has not been externally validated and is kind of unique. However we feel that the system is valid as it generally encompasses and closely follows the definitions that were used by the original seven methodologies.

Implications of Study

Analysis of these eleven international guidelines suggests that currently a large body of recommendations concerning blood component therapy is based solely on "low" quality evidence. Clearly there is a significant scarcity of strong evidence as well as clearly explicit recommendations to guide clinician practice of transfusion of blood products. In addition, many of the guidelines are not clear in reporting their methods of literature search, working group composition, and evidence review process. There is also a lack of consistency in current guidelines' use of evidence grading methodologies. This adds confusion to the interpretation of the recommendations generated for clinicians and applications of guidelines.

The use of different grading methodologies generates discrepancies in recommendations. The use of multiple and different grading methodologies does not allow for clinicians to readily compare recommendations generated from guidelines. In addition, each methodology systems assigns quality of evidence based on a variety of factors and thus can result in varying strength of recommendations for the same intervention even though derived from the similar data. These multiple recommendations with varying strengths from guidelines can translate to inconsistencies in practices amongst practitioners.

This study demonstrates that there currently is lack of robust and methodologically clear transfusion guidelines. Quality randomized controlled trials should be conducted especially with regards to the appropriate use and safety of fresh frozen plasma, cryoprecipitate and platelets. In addition, the use of multiple evidence grading methodologies creates discrepancies in recommendations and confusion amongst clinicians. Under these circumstances, it seems logical that future directions with guideline development should be aimed at the utilization of a universal methodology system to grade evidence and classify recommendations. Moreover, there

should be more integration of surgical subspecialty physicians in working group panels in the development of guideline recommendations. In conclusion, future research should also be stimulated and directed at providing more abundant and high quality evidence regarding the use and safety of blood components in the perioperative setting.

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