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A Comparison Of Blood Transfusion Practice Guidelines: What Quality Of Evidence Is Being Utilized To Develop Transfusion Guideline Recommendations?

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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 in the United States.[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 procedure
Red 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 hemoglobin 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 in the United States 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 populations in the United States.[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 thesis, 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 2010 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 2010.

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 thesis are described and defined in table 3. The terms “strong,” “intermediate,” and “low” grade of recommendation as used in this thesis 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

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Results

The bibliographic search conducted was limited to articles written in the English language published during the period from January 2005 to October 2010. 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
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

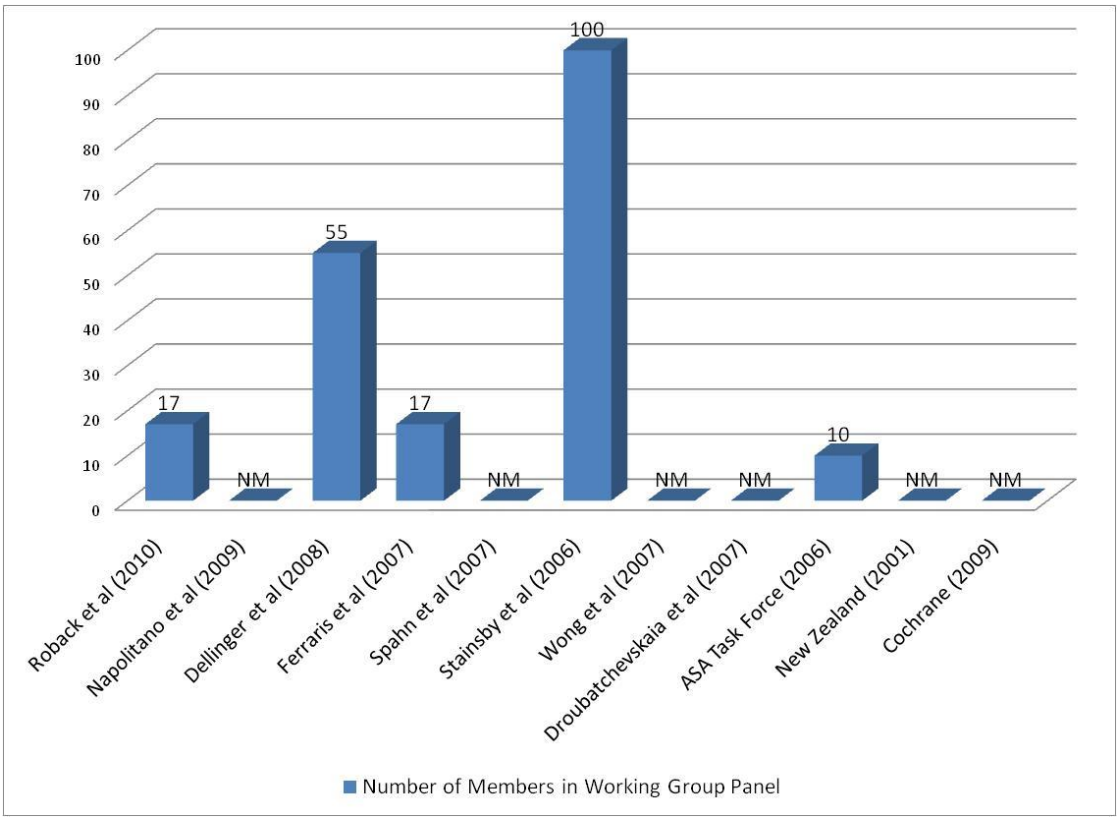


Table 6 and figure 2 report the number of medical specialties represented in each working group panel for the eleven guidelines. Six of the eleven guidelines reported having a panel member specialized in internal medicine and/or critical care medicine. Five of the eleven guidelines reported having a 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.

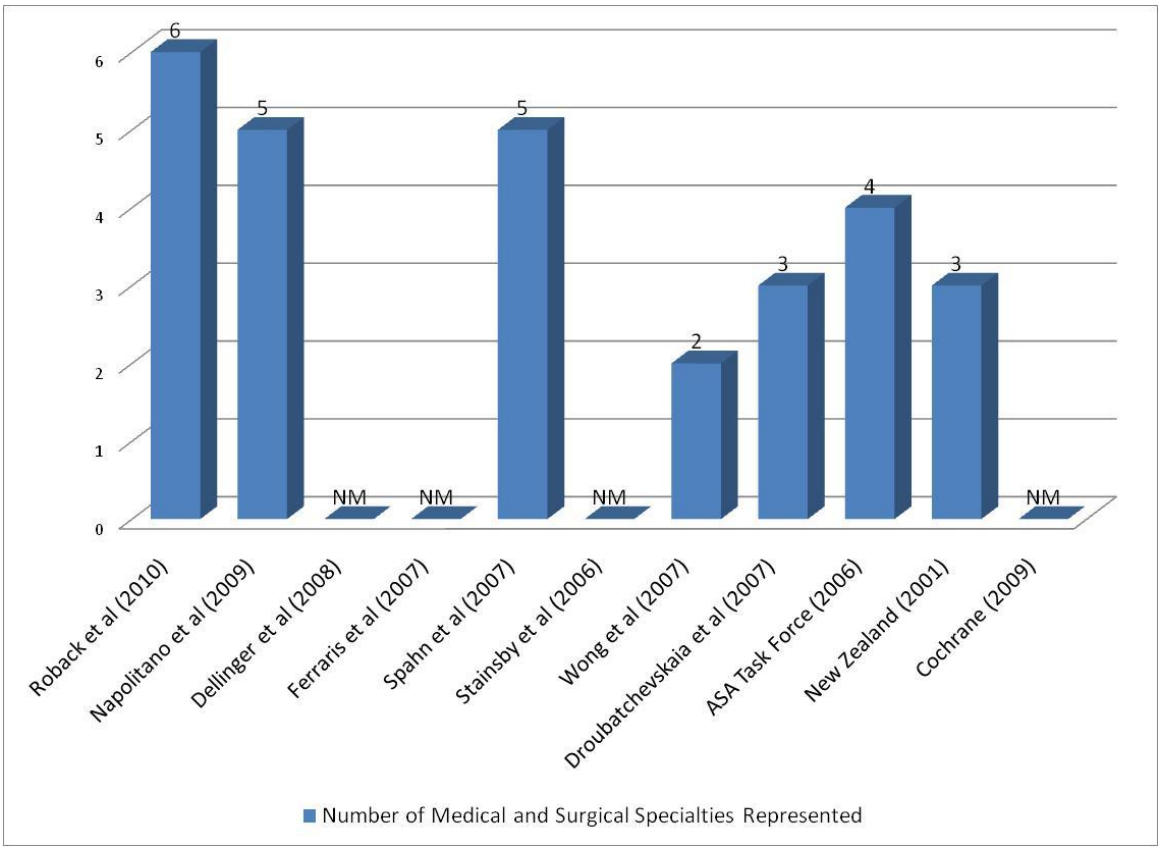
One of eleven guidelines reported five medical specialties represented, three of eleven guidelines reported four medical specialties represented, one of eleven guidelines reported three medical specialties represented, two of eleven guidelines reported two medical specialties represented, and two of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

("NM " indicates not mentioned)

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

("NM " indicates not mentioned)

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
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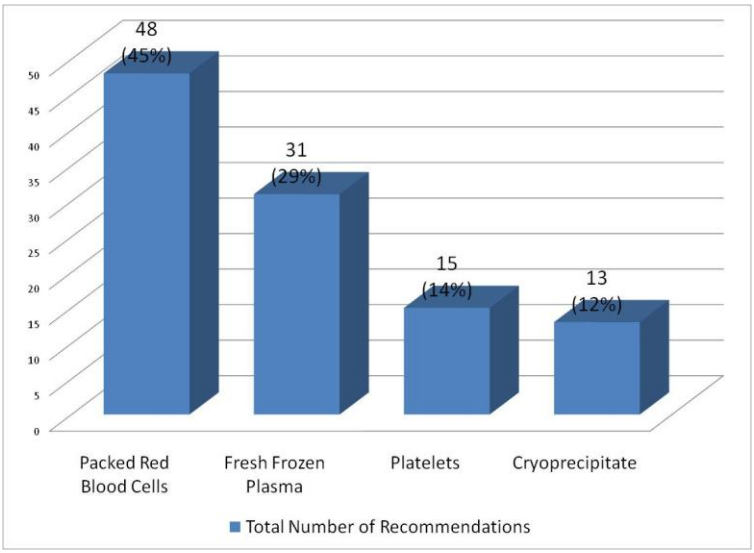
Practice Guideline Recommendations

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

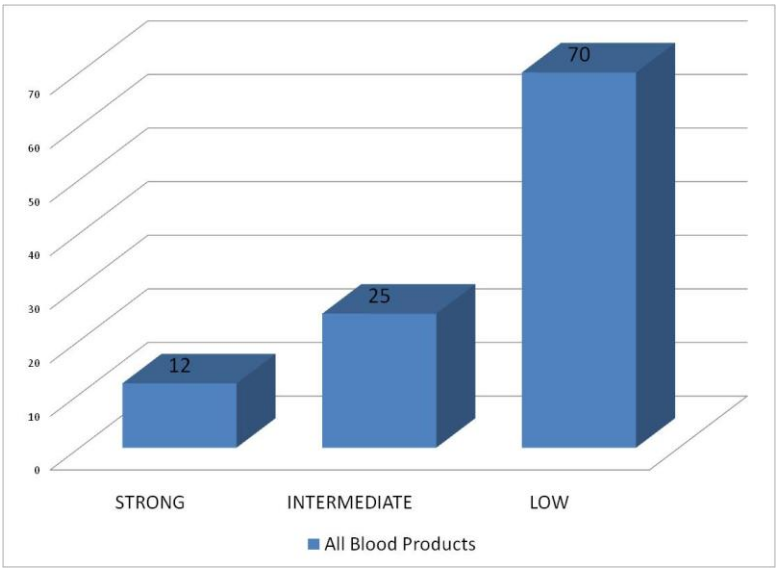


Of the 107 recommendations, table 11 and figure 4 demonstrate that only 12 (11.21%) recommendations were generated from "strong" level evidence, 25 (23.36%) recommendations were generated from "intermediate" level evidence, and 70 (65.42%) recommendations were generated from "low" level evidence.

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

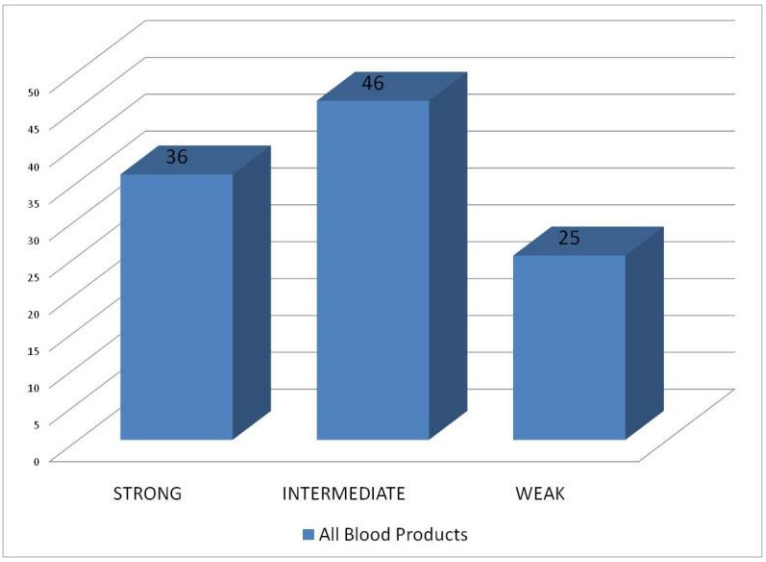


Of the 107 recommendations, table 12 and figure 5 demonstrate that 36 (33.64%) recommendations were classified as a "strong" recommendation to perform the intervention, 46 (42.99%) recommendations were classified as an "intermediate" recommendation to perform the intervention, and 25 (23.36%) recommendations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

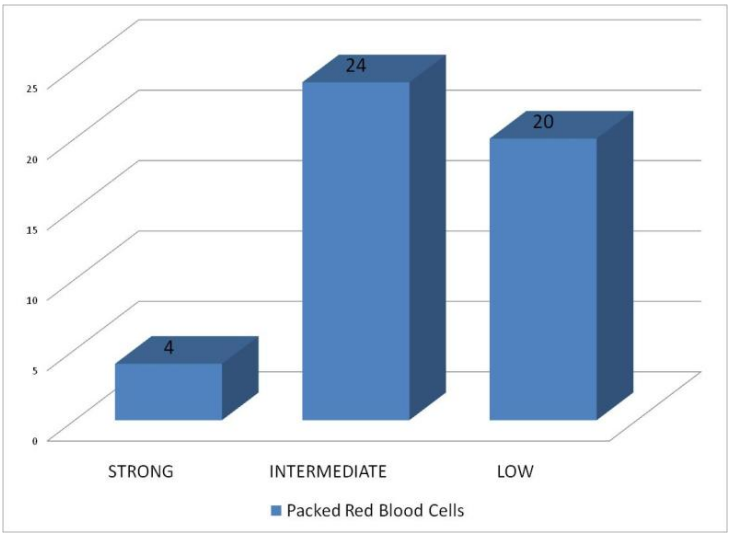
Figure 5. Strength of Recommendations for All Blood Products



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

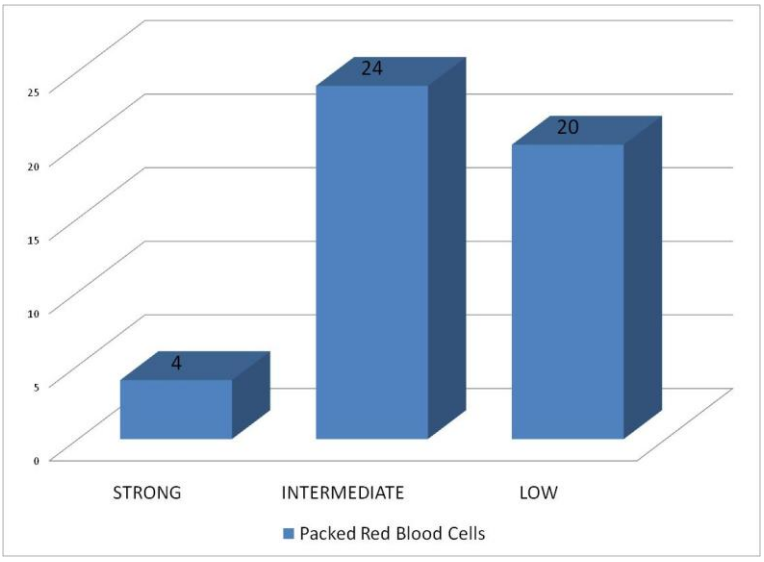
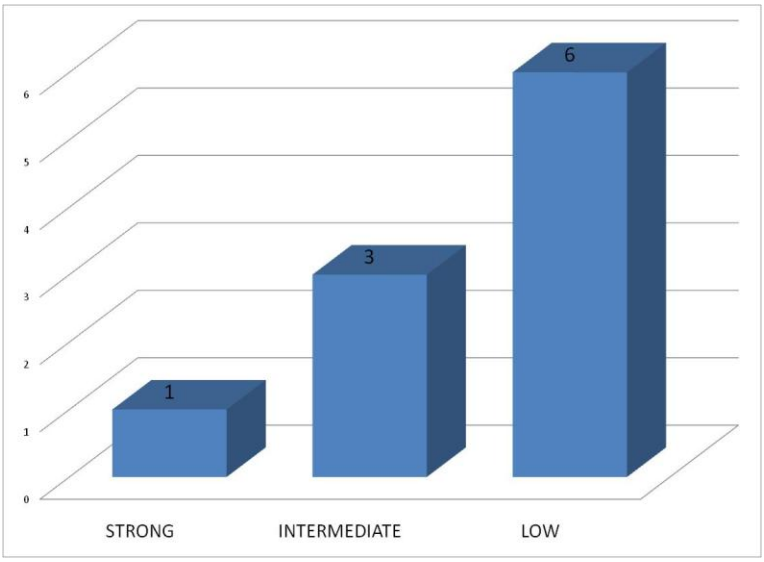


Figure 8. Level of Evidence for "Strong" Recommendations regarding use of RBC



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 anemic 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 with

moderate 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]

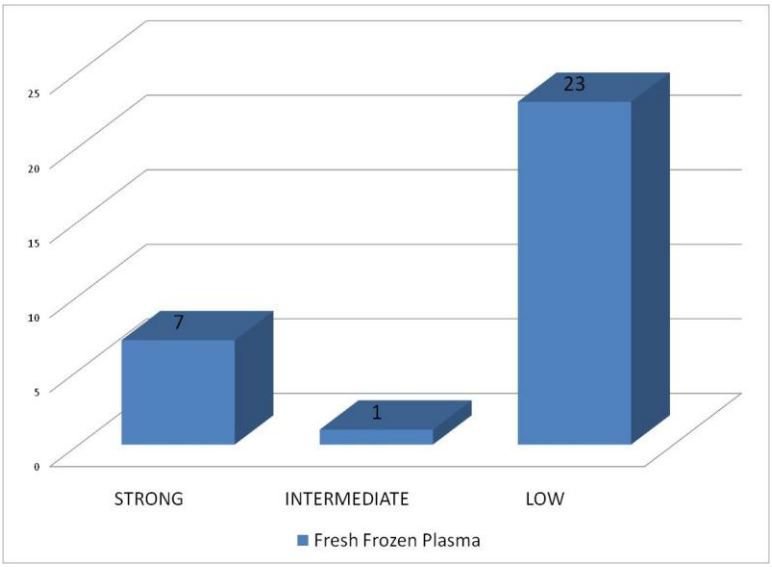
Table 16. Guidelines recommending transfusion threshold of Hb ≠ 10 g/dL

Organization	Recommendation	Evidence
Napolitano (USPTF)	Level 2 (reasonable scientific evidence and strong expert opinion)	Class 2, Class 3 (Strong prospective and retrospective analysis, retrospective data collection)
Ferraris (ACC/AHA)	Class 3 (Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases harmful)	C (Consensus opinion of experts)
British Columbia (AHCPR)	Grade C (Body of evidence provides some support for recommendation but care should be take in its application)	Level IV (Evidence obtained from case series, either post-test or pretest and post-test)
New Zealand (NHMRC)		Level I (Evidence obtained from a systematic review of all relevant RCT)
ASA	Strongly agree	Insufficient

Recommendations Regarding Clinical Use Fresh Frozen Plasma

Table 10 demonstrates that a total of 31 of the 107 recommendations were relevant to fresh frozen plasma use. Of the 31 recommendations, table 11 and figure 9 demonstrate that 7 (22.58%) recommendations were generated from "strong" level of evidence, 1 (3.23%) recommendation was generated by "intermediate" level evidence, and 23 (74.19%) recommendations generated by "low" level evidence.

Figure 9. Level of Evidence Utilized for Fresh Frozen Plasma Recommendations



Of the 31 recommendations, table 12 and figure 10 demonstrate that 9 (29.03%) of the recommendations were classified as a "strong," 10 (32.26%) recommendations were classified as an "intermediate," and 12 (38.71%) recommendations were classified as a "weak." Of the 9 "strong" recommendations, none of recommendations was based on "strong" level of evidence, 3 (33.33%) recommendations based on "intermediate" level of evidence, and 6 (66.67%) recommendations based on "low" level of evidence (Figure 11).

Figure 10. Strength of Recommendations for Fresh Frozen Plasma

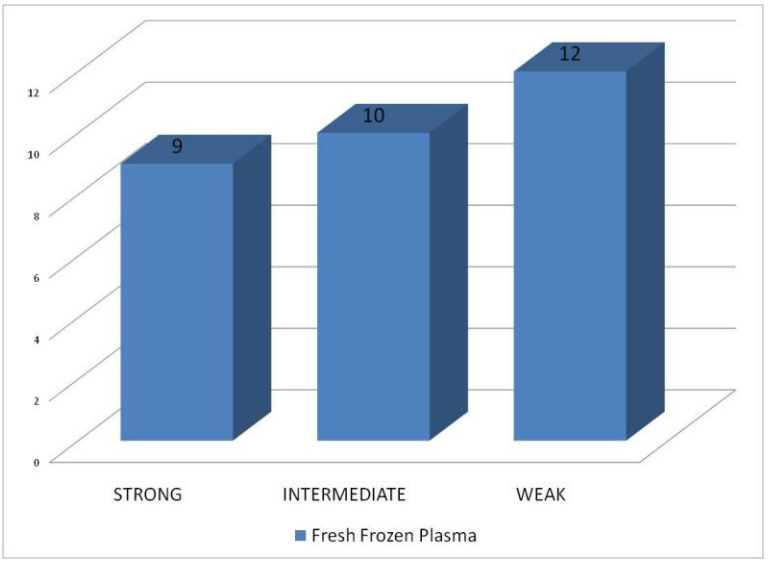
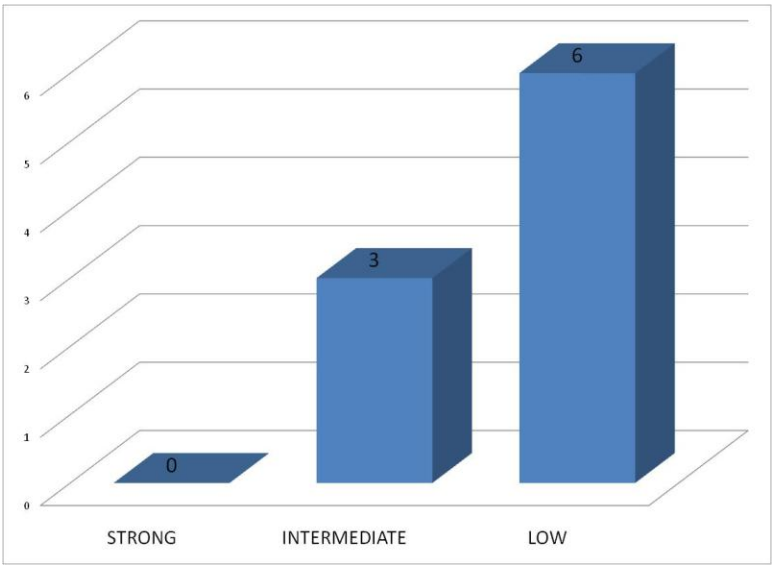


Figure 11. Level of Evidence for "Strong" Recommendations regarding FFP



Appendix table 2 summarizes recommendations for the clinical use of fresh frozen plasma from the eleven international guidelines. Six of 10 guidelines mention recommendations on the use of fresh frozen plasma, however only 3 of these six

guidelines give detailed recommendations on its use. Three guidelines **recommend** transfusion and treatment with plasma in trauma patients requiring massive transfusion (Roback, Moderate) especially to maintain INR and PTT <1.5 (Table 17) or upper limit of the reference range or increase fibrinogen level to 1g/L (British Columbia, Grade B Level IIB), and to patients with massive bleeding or significant bleeding complicated by coagulopathy (PT or aPTT >1.5 control) (Table 17) (Spahn, Grace 1C). [48,57,58] However in other trauma settings, Roback et al **cannot recommend for or against** transfusion of plasma at a plasma:RBC ratio of 1:3 or more during massive transfusion (Low) or for the use of plasma transfusion in surgical/trauma patients in the absence of massive transfusion (Very low). [50]

Table 17. Guidelines recommending transfusion threshold of PT/aPTT >1.5

Organization	Recommendation	Evidence
Spahn (GRADE)	Strong / Grade 1 (Recommend; benefits do or do not outweigh harm and burden)	Class C (Low; current evidence from observational studies, case series or just opinion)
British Columbia (AHCPR)	Grade C (Body of evidence provides some support for recommendation but care should be take in its application)	Level IV (Evidence obtained from case series, either post-test or pretest and post-test)

Roback et al **recommended** that plasma be transfused in patients with warfarin anticoagulation-related intracranial hemorrhage (low), and in the Australian guidelines it suggested that transfusion also in the presence of potentially life-threatening bleeding (Level IV), but Roback et al **cannot recommend for or against** transfusion of plasma to reverse warfarin anticoagulation in patients without intracranial hemorrhage (very low). [50,55]

The British Columbian and Australian guidelines give specific recommendations regarding congenital and acquired deficiencies. Fresh frozen plasma is **indicated** for

single factor congenital deficiencies where a specific or combined factor concentrate is not available (British Columbia, Grade C Level IV; Australia. Level IV). [48,55] Fresh frozen plasma is also **indicated** for multiple factor deficiencies, hypo/dysfibrinogenemias, and/or disseminated intravascular coagulopathy associated with severe bleeding (British Columbia, Grade C Level IV; Australia, Level IV). [48,55] Use of fresh frozen plasma for treatment of thrombotic thrombocytopenia purpura is controversial, but transfusion of fresh frozen plasma may **be initiated** for treatment (British Columbia, Grade B Level IB; Australia Level IV). [48,55] For vitamin K deficiency, fresh frozen plasma **should not** be used to correct inadequate vitamin K intake even if clotting factors are prolonged unless urgent invasive procedures are required or the patient is bleeding (British Columbia, Grade B Level IIA). [48] With regards to liver disease, especially in the setting of a liver biopsy with a patient with marked coagulopathy, the prophylactic use of frozen plasma **may be utilized** prior to a procedure based on the clinician's judgment (British Columbia, Grade B Level IIA; Australia Level IV). [48,55]

In the British Columbia guidelines fresh frozen plasma **should not be routinely used** in cardiopulmonary bypass surgery (British Columbia, Level IIB). The Australian guideline **recommends** the use of frozen plasma only in the presence of bleeding and abnormal coagulation following cardiac bypass surgery (Australia, Level IV). [48,55] Fresh frozen plasma is generally **not considered appropriate for the treatment** of hypovolemia, plasma exchange procedures or treatment of immunodeficiency states (Australia, Level IV). [55]

Recommendations Regarding Clinical Use of Platelets

Table 10 demonstrates that a total of 15 of the 107 recommendations were relevant to platelet use. Of the 15 recommendations, table 11 and figure 12 demonstrate that 1 (9.67%) recommendation was generated from "strong" level of evidence, no recommendation was generated by "intermediate" level of evidence, and 14 (93.33%) recommendations were generated by "low" level of evidence.

Figure 12. Level of Evidence Utilized for Platelet Recommendations

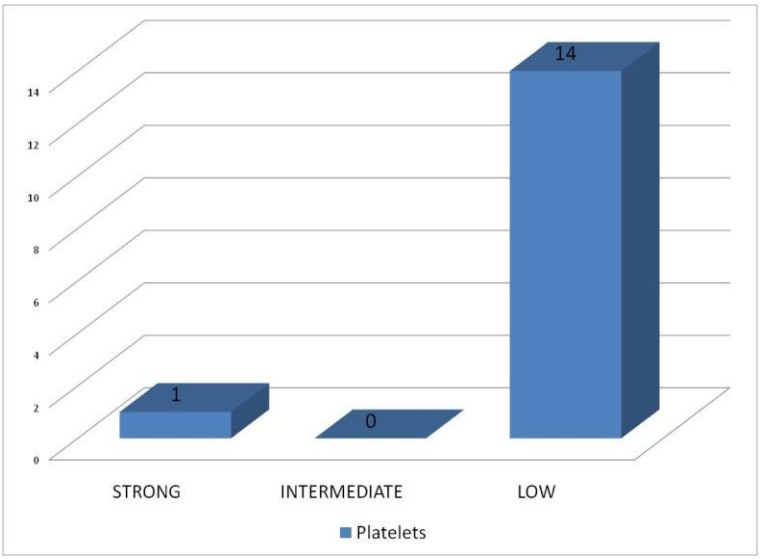


Table 12 and figure 13 demonstrate that 10 (66.67%) recommendations were classified as "strong" recommendations, no recommendations were classified as an "intermediate", and 5 (33.33%) recommendations were classified as "weak" recommendations. Of the 10 "strong" recommendations, 1 (10.00%) recommendation was based on "strong" level of evidence, and 9 (90.00%) recommendations based on "low" level of evidence (Figure 14).

Figure 13. Strength of Recommendations for Platelets

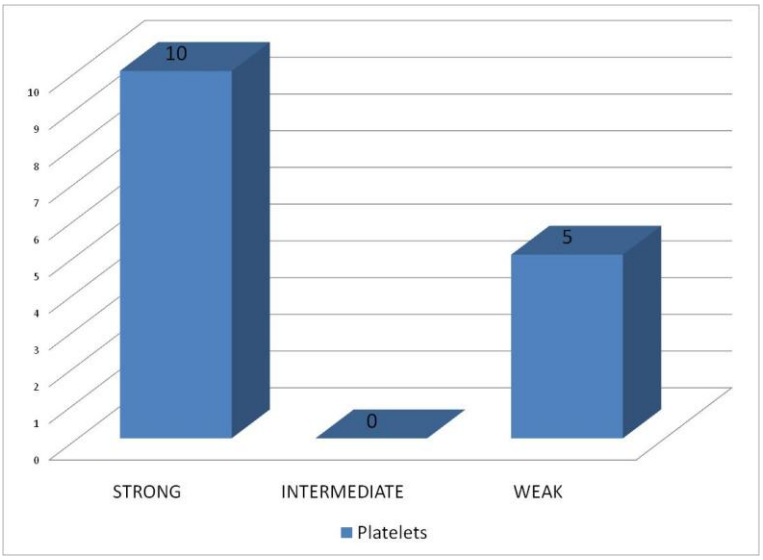
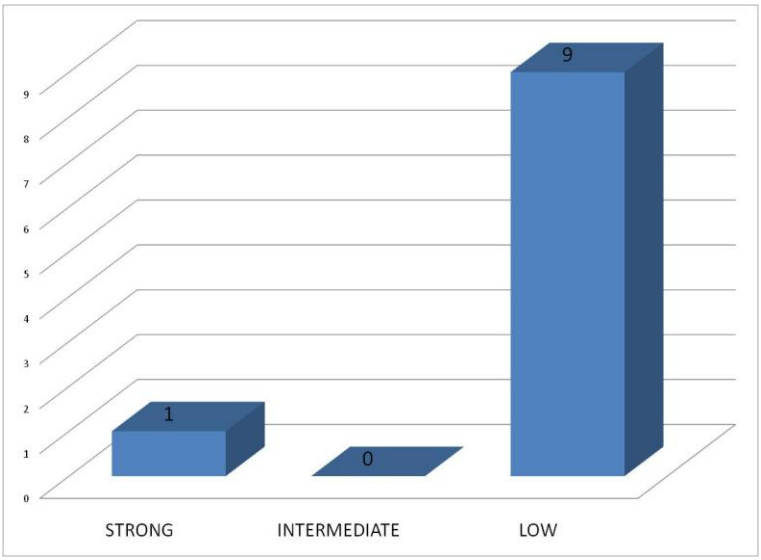


Figure 14. Level of Evidence for "Strong" Recommendations regarding use of Platelets



Appendix table 3 summarizes the eleven international guideline recommendations for the clinical use of platelets. Four of the 10 guidelines reviewed commented in the use of platelets with varying triggers for transfusion. Dellinger et al **weakly recommended** administering platelets when counts <5,000/mm^3 regardless of bleeding, counts 5,000-30,000/mm^3 if there is a significant bleeding risk, and

</=50,000/mm^3 if prior to surgery or invasive procedures (Level 2D Weak). [56] The Australian guideline also **recommends** maintaining counts >50,000/mm^3 for patients undergoing surgery or invasive procedures (Australia, Level IV), counts >50,000/mm^3 in the setting of massive hemorrhage (Australia, Level IV), and counts >100,000/mm^3 in presence of diffuse microvascular bleeding (Australia, Level IV). [55]

There are similar platelet transfusion thresholds recommendations for patients with trauma or brain injury. The British Committee **recommends** maintaining a count >75,000/mm^3 in for a majority of patients, with a higher target count of 100,000/mm^3 for patients with multiple high-velocity trauma or central nervous system injury (British, Level IV Grade C).[59] Moreover, Spahn et al **recommends** administering platelets for a count >50,000/mm^3 for a majority of patients (Grade 1C), and counts >100,000/mm^3 for patients with multiple trauma who are severely bleeding or have traumatic brain injury (Grade 2C). [51]

As prophylaxis, the Australian guideline **recommends** transfusion if counts <10,000/mm^3 in bone marrow failure without risk factors, or counts <20,000/mm^3 in the presence of bone marrow failure with risk factors (e.g., fever, antibiotics, systemic hemostatic failure) (Level II). [55] They also state that platelets are **not generally considered appropriate** to treat immune-mediated platelet destruction, thrombotic thrombocytopenia purpura, hemolytic uremic syndrome, or drug-induced or cardiac-bypass-induced thrombocytopenia without hemorrhage (Level IV). [55]

Recommendations Regarding Clinical Use of Cryoprecipitate

Table 10 demonstrates that a total of 13 of the 107 recommendations were relevant to packed red blood cell use. Of the 13 recommendations, table 11 and figure 15 demonstrate that no recommendations was generated from "strong" level of evidence or "intermediate" level evidence, and all 13 (100.00%) recommendations were generated by "low" level of evidence.

Figure 15. Level of Evidence Utilized for Cryoprecipitate Recommendations

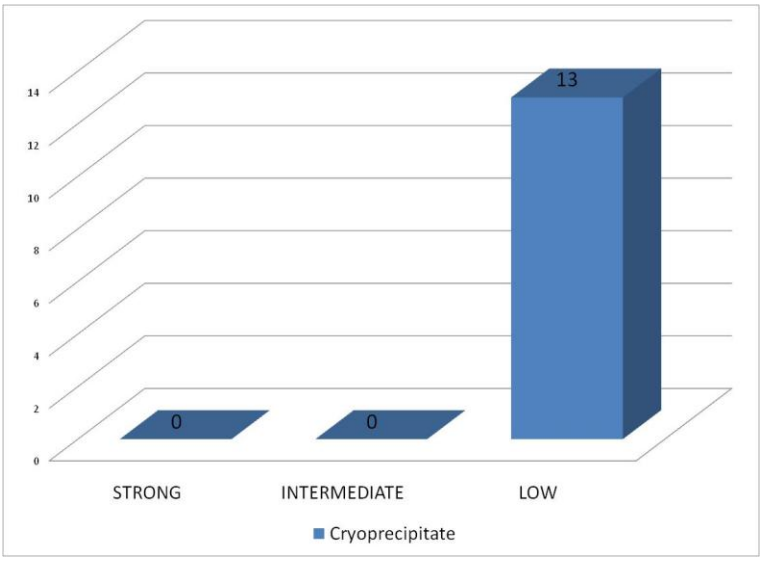
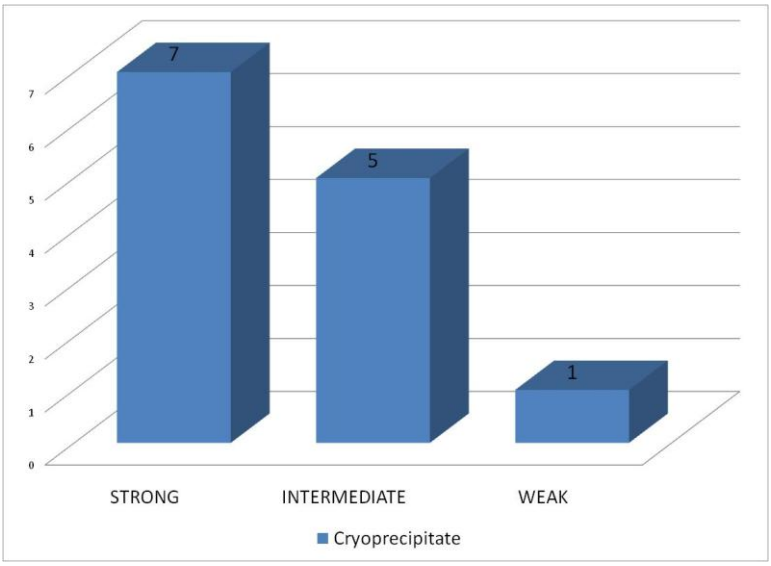


Table 12 and figure 16 demonstrate that 7 (53.85%) recommendations were classified as "strong" recommendations, 5 (38.46%) recommendations were classified as "intermediate," and 1 (7.69%) recommendation was classified as a "weak" recommendation. All 7 "strong" recommendations regarding use of cryoprecipitate were based on "low" level of evidence.

Figure 16. Strength of Recommendations for Cryoprecipitate



Appendix table 4 summarizes recommendations for the clinical use of cryoprecipitate from the eleven international guidelines. Four of 10 guidelines mention indications and recommendations for the use of cryoprecipitate. Three of the guidelines specify that the transfusion threshold for cryoprecipitate should be used to maintain fibrinogen >1g/L (British, Grade C Level IV; British Columbia, Grade C Level I; Spahn, Grade 1C).[51,60] The use of transfusion is **considered** appropriate in patients with fibrinogen deficiency, inherited or acquired hypofibrinogenemia, dysfibrinogenemia or disseminated intravascular coagulation where there is clinical bleeding, during an invasive procedure, or trauma (British Columbia, Grade C Level IV; Australia, Level IV; Spahn, Grade 1C). [51,55,60]

All guidelines advocate the use of cryoprecipitate in the setting of hemophilia, von Willebrand's disease, or deficiencies or factor XIII or fibronectin. The advisory group of British Columbia **recommends** that cryoprecipitate can be used in patients with von

Willebrand's disease if they are unresponsive to desmopressin (British Columbia, Grade C, Level IV), used in hemophilia A patients in areas where Factor VIII:C concentrates are not available (British Columbia, Level IV), and use in patients with FXIII deficiency where specific factor concentrate is usually not readily available in emergent situations (British Columbia, Grade C, Level IV). [60] The Australian guideline also does **not generally consider it appropriate** to use cryoprecipitate in the treatment of hemophilia, von Willebrand's disease, or deficiencies of factor XIII or fibronectin unless alternative therapies are unavailable (Level IV). [55]

In addition, clinical algorithms incorporate the use of cryoprecipitate to manage signs or symptoms of intracranial bleeding in patients during or after administration of tPA (British Columbia, Grade C Level IV). [60] Cyroprecipitate is **not recommended** in sepsis, as recent controlled trials failed to improve renal and pulmonary function and peripheral hemodynamics in critically ill septic patients (British Columbia, Grade A Level IV), and is not recommended in the use of preparation for fibrin glue (British Columbia, Grade B and C Level III and IV). [60]

Discussion

Guidelines Working Group Panel

Analysis of the guidelines demonstrates that a significant proportion of the guidelines do not mention the total number of members involved, members representing different medical and surgical specialties or societies, and consulting methodologists comprising the guideline working group (Table 5, Table 6, Figure 1, and

Figure 2). The majority of the guidelines reviewed list the medical and surgical specialties represented in their working group (Table 5 and 6). Only half of the guidelines specified medical specialties such as hematology and internal medicine/critical care medicine in their methods (Table 6 and figure 2). However, only a minority of the guidelines' working group panels included members trained in anesthesiology, emergency medicine, surgery (thoracic/trauma) or obstetrics. The inclusion of such specialties is important as physicians in those fields frequently deal with patients who can present or develop significant bleeding and require massive transfusion. It is important to note that there was no mention of members in the working panel representing orthopedic surgery, vascular surgery, oncologic surgery, solid organ transplant surgery and neurosurgery. The exclusion of these surgical subspecialties is significant, as members of these specialties regularly use transfusion of blood components. It is important to include them, to get their perspective, give credibility to the guidelines and for the uniformity in clinical care.

More surprisingly, there is even less inclusion of methodologists in the process of guideline development. Only two of eleven guidelines specifically mention that they consulted methodologists and included them in their working group (Table 5). It is vital to know if methodologists are involved in the process of guideline development, as they are trained in critically appraising evidence, such as assessing the significance of outcomes and factors affecting quality of evidence. In addition, methodologists are also trained in determining the applicable translation of the evidence in to clinical practice and grading strength of recommendations, such as assessing risks versus benefits.

Evidence and Systematic Reviews Utilized to Generate Guidelines

There is a lack of clarity in the methods section about the nature of literature review employed by the eleven guidelines (Table 7 and 8). A majority of guidelines did not reveal the databases utilized for their literature search or mention the study designs of the evidence they utilized to base their recommendations.

Methodology Utilized to Grade Evidence

The six methodologies employed by the eleven international guidelines reviewed have both their merits and their limitations. The details of the inclusion criteria and definitions for classification of grading quality of evidence and strength of recommendations for each methodology as listed below (Tables 18-32).

Table 18. AHRQ Grading of Quality of Evidence

Grade	Definition
1a	Evidence obtained from meta-analysis of RCT
1B	Evidence obtained from at least one RCT
2A	Evidence obtained from at least one well-designed controlled study without randomization
2B	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
4	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Table 19. AHRQ Strength of Recommendations

Strength	Definition
A	Requires at least one RCT as a part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels 1A, 1B)
B	Requires the availability of well conducted clinical studies but no RCT on the topic of recommendation (Evidence levels 2A, 2B, 3)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

The USPSTF methodology involves reviewing evidence, estimating the magnitude of benefits and harms for each preventive service, reaching a conclusion about the net benefit for each preventive service, and issuing a recommendation about the service(Tables 20-23). This methodology does not include the type of study design as a factor influencing grading of evidence or provide recommendations when there is little or low evidence available.

Table 20. USPSTF Grading Definition After May 2007

Grade	Definition	Recommendation
A	Recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	Recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	Recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
D	Recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	Concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Table 21. USPSTF Level of Certainty After May 2007

Level of Certainty	Definition
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Table 22. USPSTF Grading Definition Prior to May 2007

Grade	Definition	Recommendation
A	Strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms*.	Strongly recommended.
B	Recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms*.	Recommended.
C	Makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation*.	No recommendation.
D	Recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits*.	Not recommended.
I	Concludes that the evidence is insufficient to recommend for or against routinely providing [the service].*Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined*.	Insufficient evidence to make recommendation.

Table 23. USPSTF Quality of Evidence Prior to May 2007

Quality of Evidence	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

The ACC/AHA methodology in Table24 involves collection and grading of evidence for guideline development, which allows one to draw conclusions (i.e., guideline recommendations) that are supported by data (i.e., level of evidence). The ACC/AHA Task Force recommends either assigning the Classification of Recommendation and Level of Evidence when writing the recommendations, or rather to state the recommendation and assign the classification afterwards after re-examining data. Assigning a Classification of Recommendation and Level of Evidence, aids to provide a more descriptive and quantitative criteria for evidence ratings. In addition, with the ACC/AHA methodology involving Classification of Recommendations and Levels of Evidence, any combination of the two rating systems is possible.

Designation of Level of Evidence B or C should not be construed as implying that the recommendation is weak. It merely implies that certain clinical questions addressed in the guidelines do not lend themselves to experimentation or have not yet been addressed by high quality investigations. The clinical questions may be relevant or

important enough that it is addressed in the guidelines, even though randomized controlled studies may not be available to answer and support the query.

Table 24. AHA/ACC Grading of Evidence and Strength of Recommendation Classification

	Size of Treatment Effect				
Estimate of Certainty (Precision) of Treatment Effect		**Class I** Benefit >>>Risk Procedure/Treatment SHOULD be performed/administered	**Class IIA** Benefit>>>Risk Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment	**Class IIB** Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful IT IS NOT UNREASONABLE to perform procedure/administer treatment	**Class III** Risk ≥ Benefit Procedure/Treatment should NOT be performed/administered since IT IS NOT HELPFUL and MAY BE HARMFUL
	Level A Multiple (3-5) population risk strata evaluated General consistency of direction and magnitude of effect	Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses	Recommendation that procedure or treatment not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
	Level B Limited (2-3) population risk strata evaluated	Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or non-randomized studies	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or non-randomized studies	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or non-randomized studies	Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or non-randomized studies
	Level C Very limited (1-2) population risk strata evaluated	Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care	Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard –of-care	Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care	Recommendation that procedure or treatment not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

The NHMRC utilizes a system that allows also for Levels of Evidence and Grades of Recommendation (Tables 25 and 26). The classification system for evidence assigns levels of evidence according to the type of research question, recognizing the importance of appropriate research design to that specific clinical question in guideline development. Grading of recommendations is ascribed not only by the level of evidence, but takes into consideration the quality of the study and the likelihood that the results have been affected by bias during its conduct, the consistency of its findings to those from other studies, the clinical impact of its results, and generalizability of the

results to the population for whom the guideline is intended, and the applicability of the results to the Australian or local healthcare system. Thus the grade of the recommendation is based on an overall assessment of all these components of the body of evidence being assessed.

Table 25. NHMRC Evidence Hierarchy

LEVEL	Intervention	Diagnostic Accuracy	Prognosis	Etiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomized controlled trial
III1	A pseudo-randomized controlled trial (ie, alternate allocation or some other method	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudo-randomized controlled trial (ie, alternate allocation or some other method)
III2	A comparative study with concurrent controls: Non-randomized experimental trial, Cohort study, Case-control study, Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III1 evidence	Analysis of prognostic factors amongst persons in a single arm of randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomized experimental trial, Cohort study, Case-control study
III3	A comparative study without concurrent controls: Historical control study, Two or more single arm study, Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study, Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Table 26. NHMRC Body of Evidence Matrix and Grades of Recommendation

Component	Grade A Excellent Body of evidence can be trusted to guide practice	Grade B Good Body of evidence can be trusted to guide practice in most situations	Grade C Satisfactory Body of evidence provides some support for recommendations but care should be taken in its application	Grade D Poor Body of evidence is weak and recommendation must be applied with caution
Evidence Base	One or more level I studies with a low risk or bias or several level II studies with a low risk bias	One or two level II studies with a low risk of bias or a systematic review/several level III studies with low risk bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/systematic reviews with a high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical questions	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalizability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalize to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

The ASA uses specific terms to specify the grading of evidence in their formulation of recommendations. When sufficient numbers of studies are available for evaluation, the terms in table 27 are used to describe the strength of the findings. When the ASA describes the lack of scientific evidence in the literature, it uses the terms listed in table 28. When information is collected from consultants and members of the

ASA, the terms used to describe survey responses for any issue are represented in Table 29. The survey responses are solicited on a five-point scale, ranging from 1 (strongly disagree) to 5 (strongly agree), with the score of 3 being equivocal.

Table 27. ASA Grading of Evidence

Support	Meta-analysis of a sufficient number of randomized controlled trials indicates a statistically significant relationship (P<0.01) between a clinical intervention and a clinical outcome.
Suggest	Information from case reports and descriptive studies permits inference of a relationship between an intervention and an outcome. This type of qualitative information does not permit a statistical assessment of significance.
Equivocal	Qualitative data are not adequate to permit inference of a relationship between an intervention and an outcome and (1) there is insufficient quantitative information or (2) aggregated comparative studies have found no significant differences among groups or conditions.

Table 28. ASA Strength of Recommendations

Silent	No identified studies address the relationship of interest.
Insufficient	There are too few published to investigate a relationship between an intervention and outcome.
Inadequate	The available studies cannot be used to assess the relationship between an intervention and an outcome. There studies either do not meet the criteria for content as defined in the Focus of these Guidelines or do not permit a clear casual interpretation of findings due to methodologic concerns.

Table 29. ASA Survey Responses

Strongly Agree	Median score of 5 (at least 50% of the responses are 5).
Agree	Median score of 4 (at least 50% of the responses are 4 or 4 and 5).
Equivocal	Median score of 3 (at least 50% of the responses are 3, or no other response category or combination of similar categories contain at least 50% of the responses).
Disagree	Median score of 2 (at least 50% of responses are 2 or 1 and 2).
Strongly Disagree	Median score of 1 (at least 50% of responses are 1).

The GRADE methodology, however, has become the methodology that is currently being accepted by an increasing number of organizations. The GRADE working group represents an international collaboration of guideline developers, clinicians, health service researchers, and methodologists. The GRADE system for grading the

quality of evidence comprises four steps: identifying important and critical outcomes; preliminary grading of evidence in terms of study design, quality, consistency and directness; taking in to account other factors that can increase or decrease evidence; and the overall quality of the evidence. The definition for quality of evidence is listed in Table 30. The strength of recommendation, categorized as strong, weak or conditional recommendations for or against an intervention or treatment, is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh the undesirable effects. It requires the consideration of the benefits and risks of an intervention for all patient-important endpoints, the associated values and preferences and resource use.

Other previous systems of grading rely almost exclusively on overall study design to determine quality of evidence, however in the GRADE system study design remains critical but not a sole factor in judging the quality of evidence. In the GRADE system, expert opinion is not a category of quality of evidence but rather an interpretation of existing evidence. In addition there are factors that can reduce or increase quality of evidence for each study design, that overcome the limitations of grading quality of evidence with just study design (Tables 31 and 32). This is important, as a well-designed and executed non-randomized trial or observational study, may provide better quality evidence than a poorly executed randomized-controlled trial.

Table 30. GRADE Quality of Evidence

Grade	Definition
High ⊕⊕⊕⊕	Further research is unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕◯	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low ⊕⊕◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low ⊕◯◯◯	Any estimate of effect is very uncertain.

Table 31. Factors that can reduce the Quality of the Evidence

Factor	Consequence
Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Table 32. Factors that can increase the Quality of the Evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

The advantage of the GRADE system versus other methodologies is its transparency. It considers many other factors other than study design of literature in determining the strength and quality as evidence. In addition, it generates appropriate recommendations for course of action in the setting of very little evidence available. Some of the medical professional associations that have shifted to using the GRADE system include the following international organizations listed in Appendix table 5.

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 hemoglobin < 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.

Appendix

Appendix Table 1. Summary of Guideline Recommendations and Indications for Clinical Use of Packed Red Blood Cells

	Napolitano	Dellinger	Ferraris	Spahn	British Columbia	ASA	New Zealand
Methodology	**USPTF**	**GRADE**	**ACC/AHA**	**GRADE**	**AHCPR**	**ASA**	**NHMRC**
Trigger	Hb < 7g/dl Hb </= 8 g/dl	Hb < 7g/dl Target Hb 7-9 g/dl	Hb < 6 g/dl Hb < 7g/dl	Target Hb 7-9 g/dl	Hb < 6 g/dl Maintain at Hb > 8g/dl Rarely >10 g/dl	Hb <6g/dl	Hb < 7 g/dl (if asymptomatic lower trigger appropriate) Target Hb 7-10 g/dl
Hemorrhagic shock	Hb < 7g/dl Acute hemorrhage, hemodynamic instability or inadequate oxygen delivery (except in acute myocardial ischemia) Level 1: Class 1 RCT, strong Class 2 Observational, Pro Cohort, prevalence, case-control retrospective	Hb < 7g/dl For acute hemorrhage, higher Hg level may be required					
Critically ill/mechanical ventilation	Hb < 7g/dl Patients with stable cardiac disease Avoid Hb as trigger Level 2: Class 2, Class 3						
Myocardial ischemia/cardiac disease	Acute coronary disease and anemia use trigger of Hb </= 8 g/dl Level 3	Hb < 7g/dl Higher Hb level may required					
Post-operative			Hb < 6 g/dl For cardiac operations Hb < 7 g/dl No high-level evidence				
Cardiopulmonary bypass			Hb < 6 g/dl Except in patients with cardiovascular disease, diabetes mellitus, cerebrovascular disease, carotid stenosis Hb target >/= 7 g/dl For patients at risk for critical end-organ ischemia				
Lactic acidosis		Hb < 7g/dl Higher Hb level may required					
Not indicated	Sepsis (no clear evidence transfusion increases tissue oxygenation) Traumatic brain injury and intracranial hemorrhage (no clear evidence it improves outcomes)		Unlikely to improve tissue pxygenation with Hb > 10 g/dl			Hb >10g/dl	Inappropriate when Hb > 10 g/dl

Appendix Table 2: Summary of Guideline Recommendations and Indications for Clinical Use of Fresh Frozen Plasma

	Roback	Dellinger	Spahn	British Columbia	ASA	New Zealand
Methodology	**GRADE**	**GRADE**	**GRADE**	**AHCPR**	**ASA**	**NHMRC**
Trigger	-	-	PT/aPTT < 1.5	PT/aPTT < 1.5	Elevated aPTT (agree)	-
Massive transfusion			For massive or significant bleeding complicated by coagulopathy	INR/PTT < 1.5 Fibrinogen >/= 1.0 g/L Replacement of patient's whole blood volume within 24 hours		
Trauma	Suggests for massive transfusion					
Inherited deficiencies				In emergency		Recommended before high-risk procedures
DIC				Only with active bleeding and coagulation abnl		Recommended
TTP				As interim measure, a slow infusion		Recommended
Warfarin anticoagulation/intracranial hemorrhage	Suggests transfusion			Severe bleeding or hemostasis for emergency surgery or invasive procedure		For immediate reversal in presence of life-threatening bleeding
Vitamin K deficiency				Bleeding or urgent invasive procedure		
Liver biopsy				Prophylactic measure is there is marked abnl or coagulopathy		
Not indicated	Acute pancreatitis, organophosphate poisoning, coagulopathy associated with acetaminophen overdose, intracranial hemorrhage after severe closed head injury without coagulopathy, nonsurgical non cardiac patients in ICU	To correct lab clotting abnormality unless bleeding is present or planned invasive procedure		Cardiopulmonary bypass Invasive bedside procedures with mild to moderate abnl		Hypovolemia, plasma exchange procedures, treatment of immunodeficiency states

Appendix Table 3: Summary of Guideline Recommendations and Indications for Clinical Use of Platelets

	Dellinger	Spahn	British Columbia	ASA	New Zealand
Methodology	**GRADE**	**GRADE**	**AHCPR**	**ASA**	**NHMRC**
Trigger	< 5000/mm3 regardless of bleeding	<50000/mm3	< 75000/mm3	<50000/mm3	
No bleeding					
Significant bleeding risk	5000-30000	<100000/mm3			
Pre-operative	</= 50000/mm3				<50000/mm3
Invasive procedures	</= 50000/mm3				<50000/mm3
DIC					
Trauma		<100000/mm3	<100000/mm3		
Sepsis					
Traumatic brain injury		<100000/mm3	<100000/mm3		
Bone marrow failure					<10000/mm3 without risk factors <20000/mm3 with risk factors (fever, antibiotics, systemic hemostatis failure)
Not indicated				>100000/mm3	Immune-mediated platelet destruction, thrombotic, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, drug-induced or cardiac bypass thrombocytopenia without hemorrhage

Appendix Table 4: Summary of Guideline Recommendations and Indications for Clinical Use of Cryoprecipitate

	British Columbia	ASA	New Zealand	Cochrane
Methodology	**AHCPR**	**ASA**	**NHMRC**	**SHULZ**
Trigger	Fibrinogen < 1.0 g/L	Fibrinogen <0.8g/L	-	
Inherited/acquired deficiency	< 1.0 g/L			
Dysfibrinogenemia	< 1.0 g/L			
DIC	< 1.0 g/L		When considered clinically appropriate	
Sepsis				
Invasive procedure			When considered clinically appropriate	
Trauma		Fibrinogen <0.8-1.0g/L	When considered clinically appropriate	
Intracranial hemorrhage	- During or after administration of tPA			
Hemophilia	- Used if unresponsive to desmopressin			
Von Willebrand's disease	- Used if FVIII:C concentrates not available			
Factor XIII or fibronectin deficiency	- Used if FVIII:C concentrates not available			
Not indicated	Fibrin glue. sepsis	Fibrinogen >1.5g/L	Hemophilia, von Willebrand's disease, deficiencies of XIII or fibronectin	

Appendix Table 5. Organizations that have endorsed or that are using GRADE

Organizations
World Health Organization – International
Endocrine Society – USA
American College of Chest Physicians – USA
UpToDate – Putting Clinical Information Into Practice - USA
Agenzia sanitaria regionale, Bologna – Italia
Ministry of Health and Long-term Care, Ontario – Canada
Surviving Sepsis – International
Arztliches Zentrum fur Qualitat in der Medizin – Germany
American Thoracic Society – USA
American College of Physicians – USA
The Cochrane Collaboration – International
Kidney Disease: Improving Global Outcome – International
European Society of Thoracic Surgeons – International
British Medical Journal – UK
Journal of Infection in Developing Countries – International
Agency for Healthcare Research and Quality (AHRQ) – USA
Society of Critical Care Medicine (SCCM) – USA
National Institute for Clinical Excellence (NICE) – UK
Norwegian Knowledge Centre for the Health Services – Norway
The University of Pennsylvania Health System Center for Evidence-based Practice – USA
German Center for Evidence-based Nursing “sapere aude” – Germany
Evidence-based Nursing Sudirol, Alto Adige – Italy
Society for Vascular Surgery – USA
BMJ Clinical Evidence – UK
EBM Guidelines – Finland/International
Polish Institute for EBM – Poland
European Respiratory Society (ERS) – Europe
Japanese Society for Temporomandibular Joint – Japan
National Board of Health and Welfare – Sweden
COMPUS at The Canadian Agency for Drugs and Technologies in Health (CADTH) – Canada
Infectious Diseases Society of America – USA
Spanish Society for Family and Community Medicine – Spain
Emergency Medical Services for Children National Resource Center – USA
SBU – The Swedish Council on Technology Assessment in Health Care – Sweden
The Scottish Intercollegiate Guidelines Network (SIGN) – UK
Evidence-Based Tuberculosis Diagnosis (tbevidence.org) – Canada
National & Gulf Center for Evidence Based Health Practice (NGCEBHP) – Saudi Arabia
American Society for Gastrointestinal Endoscopy – USA
European Association for the Study of the Liver – Europe
CDC’s Healthcare Infection Control Practices Advisory Committee (HICPAC) – USA
Finnish Office for Health Technology Assessment – Finland
NHS Quality Improvement Scotland – UK
The American Association for the Study of Liver Diseases – USA
The Canadian Cardiovascular Society – Canada
The World Allergy Organization (WAO) – International
Kaiser Permanente – USA
The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) – Europe
World Interactive Network Focused on Critical Ultrasound – International
Critical Ultrasound Journal – Italy
American Society for Colposcopy and Cervical Pathology – USA
The Dutch Institute for Healthcare Improvement CBO – The Netherlands
Kleijnen Systematic Reviews Ltd – UK
American Gastroenterological Association – USA
Ludwig Boltzmann Institut – Austria
Canadian Task Force on Preventative Health Care – Canada
Canadian Society of Nephrology – Canada
The National Kidney Foundation / KDOQI – USA

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