RESTRICTIVE RED BLOOD CELL (RBC) TRANSFUSION THRESHOLDS: UPDATE

An Evidence Advisory from the Penn Medicine Center for Evidence-based Practice

February 2022

Lead analyst: ..... Matthew D. Mitchell, PhD (CEP)
Clinical review: ..... Patrick J. Brennan, MD (CMO)
Project director: ..... Nikhil K. Mull, MD (CEP)

Keywords: transfusion, hemoglobin, anemia, surgery

Summary

- Published clinical practice guidelines have favored restrictive RBC transfusion thresholds. Restrictive thresholds are usually defined as a hemoglobin level in the range of 7 to 9 g/dl. No guidelines mention thresholds below 7 except for an emergency medicine guideline used in Rwanda.
- Recent systematic reviews also report restrictive transfusion thresholds in the range of 7 to 9. No reviews attempted to evaluate the safety and effectiveness of thresholds below 7. Our analysis of the evidence tables from those reviews found only two trials using a threshold below 7.
- We reviewed a representative sample of recently-published clinical studies using restrictive transfusion thresholds. Only one of them mentioned use of a threshold below 7.0.
- The three studies reporting a threshold below 7.0 g/dl were all performed in Europe and used thresholds of 6.4 g/dl (4.0 mmol/l) or 6.7 g/dl (25% hematocrit) for surgery patients with no risk factors. None of the studies provided enough information to permit assessment of the comparative safety and effectiveness of the reduced threshold compared to 7.0.

CENTER for EVIDENCE-BASED PRACTICE

Table of Contents

Summary 1
Introduction 2
Previous CEP reports 3
Table 1. Previous CEP reports on related topics 3
Current UPHS policy 4
Table 2. Links to UPHS policy documents (available to UPHS staff only) 4
Review protocol 5
Results 5
Guidelines 5
Table 3. Transfusion thresholds in recent clinical practice guidelines 6
Systematic reviews 7
Table 4. Systematic review findings 8
Primary studies 8
Conclusions 9
Methods 10
Literature Search 10
Table 5. Guideline search 10
Table 6. Evidence clearinghouse search 10
Table 7. MEDLINE search 11
Table 8. Embase search 11
Table 9. Transfusion Evidence Library search 11
Additional internal reviewers 12
Conflict of interest disclosures 12
References 12

Introduction

There has been a considerable decrease in volunteer blood donations during the COVID-19 pandemic, leading to a shortage of red blood cells (RBC) for transfusion. Thus there is interest in reducing the number of RBC transfusions given. In our previous reports on this topic, we have seen increasing support for restrictive blood transfusion thresholds, in both clinical trial results and published clinical guidelines. Based on that evidence, UPHS hospitals adopted restrictive thresholds, and consider RBC transfusion appropriate for patients whose hemoglobin levels are below 7 mg/dl.

If the 7 g/dl threshold can be reduced without undue risk to patients, the health system may conserve blood at a time of shortage. The purpose of this report is to identify clinical situations where a transfusion threshold less than 7.0 g/dl has been recommended or considered, identify any guideline recommendations for lower thresholds, and identify the evidence supporting those guidelines.

Previous CEP reports

CEP reported on transfusion thresholds in 2009-10 and again in 2015-16 (Table 1). We found increasing evidence to support use of restrictive RBC transfusion thresholds in surgery and oncology patients. Restrictive thresholds were usually defined at hemoglobin levels of 7 to 8 g/dl. There was very little evidence on the safety or effectiveness of RBC transfusion thresholds below 7.

Table 1. Previous CEP reports on related topics

Date	Topic	Findings	Link
May 2016	Transfusion thresholds for cardiovascular surgery	There is moderate-strength evidence that restrictive thresholds do not increase post-operative complications. There is continued clinical uncertainty of how low these thresholds can be set.	Evidence Review #338
Dec. 2015	Transfusion thresholds for major orthopedic surgery	Most clinical trials compared thresholds of 8 and 10 g/dl. Rates of most adverse events were not significantly affected by threshold, but infection rates were approx. 30% lower in patients managed with restrictive thresholds. Recent guidelines support more restrictive thresholds.	Evidence Review #319
Nov. 2015	Transfusion thresholds for oncology patients	NCCN guidelines recommend target hemoglobin levels of 7 to 9 g/dl in asymptomatic patients and 8 to 10 g/dl in symptomatic patients. Few RCTs of transfusion thresholds in oncology patients have been reported.	Evidence Review #320
Jan. 2010	Transfusion thresholds for orthopedic surgery	There is strong evidence that restrictive transfusion thresholds reduce blood transfusion rates. Evidence on adverse effects is weak and inconsistent.	Evidence Review #106
Dec. 2009	Transfusion thresholds for cardiovascular surgery	There is moderate-strength evidence that restrictive transfusion thresholds reduce blood transfusion rates and low-strength evidence that restrictive thresholds do not have adverse effects on morbidity and mortality.	Evidence Review #102
Feb. 2009	Indications for transfusion of blood components	Guidelines for transfusion of red blood cells, platelets, and fresh frozen plasma are summarized.	Evidence Advisory #83

UPHS staff can access full text of CEP reports through the CEP web site.
Other readers should contact CEP to request a copy of these reports.

Current UPHS policy

Table 2 lists relevant policy documents in effect at UPHS hospitals. Most of those policies recommend a transfusion threshold of 7 g/dl in medical and surgical patients. The notable exception is Chester County Hospital, where the latest guideline specifies a transfusion threshold range from 6 to 8 g/dl.

Table 2. Links to UPHS policy documents (available to UPHS staff only)

Entity	Threshold	Link
CCH	Consider transfusion when hemoglobin levels are 6-8 g/dL based on patient's complications due to inadequate oxygenation. Critical care transfusion trigger 7 g/dl when patient can tolerate this range. Consider transfusion at 8 g/dl in surgical patients with symptoms.	Transfusion guidelines (Nov. 2021)
HUP	Below 7.0 g/dl, transfusion is appropriate but not obligatory for all patients.	Policy #1-7-17 (May 2020)
LGH	General transfusion threshold of 7 g/dl or hematocrit < 21%. Threshold of 8 g/dl or hematocrit < 24% in orthopedic surgery patients, cardiac surgery patients, and patients with cardiovascular disease.	*unavailable*
PMPH	Transfusion threshold of 7.0 g/dl applies to surgical patients, outpatients, cancer patients, and patients with chronic anemia.	Transfusion guidelines (Sept 2021)
PPMC	Below 7.0 g/dl, transfusion is appropriate but not obligatory for all patients.	Policy #11.155 (Nov. 2021)
PAH	Red blood cells may be indicated with hemoglobin below 7.0 g/dl or at 7.0 to 9.0 g/dl with coronary ischemia, chronic cardiopulmonary disease, or oncology patient with anticipated hemoglobin reduction, or active bleeding.	Adult transfusion guidelines (2012)

CCH–Chester County Hospital, HUP–Hospital of the University of Pennsylvania, LGH–Lancaster General Hospital, PMPH–Penn Medicine Princeton Health, PPMC–Penn Presbyterian Medical Center, PAH–Pennsylvania Hospital

Review protocol

SPECIFIC AIM:
Report the hemoglobin level thresholds defined as "restrictive" in professional guidelines. Identify a selection of clinical studies where red blood cell transfusion thresholds below 7 g/dl are being used. Summarize outcomes of these clinical studies if evidence permits.
METHODS:
Study designs: Evidence-based clinical practice guidelines issued by professional societies and national health systems, systematic reviews, and primary clinical studies.
Inclusion and exclusion criteria:
Participants: Patients with anemia, including medical, surgical, and trauma patients.
Interventions: Use of a restrictive hemoglobin threshold less than 7 g/dl to guide transfusion of red blood cells or whole blood.
Comparisons: Use of a restrictive hemoglobin threshold of 7 g/dl.
Outcomes: Mortality, infection, complications, utilization of blood and blood products, length of stay, readmission to the hospital, costs.
Timing: Not applicable.
Setting: Not applicable.
Other: Published in English, 2017-present. Date range of search for systematic reviews and primary studies will be limited to 2020-present if sufficient evidence is found.
Data collection
Databases: NICE Evidence Search, ECRI Guidelines Trust, Cochrane Library, web sites of relevant professional organizations, Transfusion Evidence Library, MEDLINE, Embase (MEDLINE and Embase searches will be limited to guidelines only).
Data synthesis (calculation of relative risks and confidence intervals, meta-analyses, exploration of heterogeneity): Random-effects meta-analysis following Cochrane methods if quantity and homogeneity of data permit, otherwise qualitative analysis.
NOTE: CEP standard review methods, including scales for quality assessment of guidelines, systematic reviews, and primary studies can be found in the Methods section of the CEP web site.

Results

Guidelines

Our searches found broad and representative clinical practice guidelines relating to RBC transfusion thresholds (Table 3). We also include guidelines from the evidence table of a recent systematic review by Baker et al. (1). Most of these guidelines defined a restrictive transfusion threshold as 7.0 g/dl hemoglobin level, and none of them discussed lower thresholds. Since none of the guidelines address the key question of indications for a hemoglobin threshold lower than 7.0, we omit our usual appraisal of guideline quality.

Although they are too old to meet our protocol, AABB guidelines are included as they are cited in Chester County Hospital transfusion guidelines. Guidelines from the Joint United Kingdom (UK)

Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (2) have not been updated since 2014, but we reviewed them and found that all RBC transfusion thresholds reported in the guideline were in the range of 7.0 to 8.0 g/dl. National Blood Authority guidelines in Australia are under review; while the review questions include restrictive thresholds, no specific numeric hemoglobin thresholds were reported.

A cohort study of emergency department patients in Rwanda (3) reports that the guidelines in that country recommend RBC transfusion for patients with hemoglobin levels of 5.0 g/dl or less or whose condition is unstable. The original guideline (4), is more detailed, and recommends different thresholds for different clinical situations. The 5.0 g/dl hemoglobin threshold is for patients with chronic anemia; there is also a threshold of 6.0 g/dl for stable patients with upper or lower GI bleeding. Evidence is not cited to support those recommendations, and their applicability to a health care system with greater resources is questionable.

Table 3. Transfusion thresholds in recent clinical practice guidelines

Organization	Indication for transfusion	Recommended threshold (†)	Comment
American College of Gastroenterology 2021 (5)	Upper GI bleed	7.0	Conditional recommendation, low-quality evidence. Update to lower GI bleeding guidelines in progress.
European Society of Gastrointestinal Endoscopy 2021 (6)	Lower GI bleed	7.0 without CAD 8.0 with CAD	Strong recommendation, low quality evidence.
European Society of Intensive Care Medicine 2021 (7)	Critical care (bleeding)	7.5 without CAD 8.0 with CAD	Conditional recommendation, low certainty.
Society of Thoracic Surgeons 2021 (8)	Cardiac surgery	No threshold	A restrictive transfusion strategy is recommended in preference to a liberal transfusion strategy, but specific restrictive thresholds were not specified.
European Society of Intensive Care Medicine 2020 (9)	Critical care (not bleeding)	7.0	Strong recommendation, moderate certainty.
Association of Anaesthetists (UK) 2021 (10)	Hip fracture	8.0 without CAD 10.0 with CAD	Guideline applies to frailer patients. Fitter patients may be able to tolerate lower Hgb.
Canadian Cardiovascular Critical Care Society 2020 (11)	ECMO	7.0 to 7.5	Based on ELSO guideline. Applies to patients who are not bleeding.
British Society of Gastroenterology 2018 (12)	Lower GI bleed	7.0 without CAD 8.0 with CAD	Strong recommendation, low quality evidence.
Canadian Hepato-Pancreatico-Biliary Association 201 (13)	Liver resection	7.0 without CAD 8.0 with CAD	Evidence not graded.
European Society of Medical Oncology 2018 (14)	Cancer	7.0 to 8.0	Strong or moderate evidence, limited clinical benefit.
Frankfurt Consensus Conference 2018 (15)	Critical care (clinically stable)	7.0	Strong recommendation, moderate certainty.
	Cardiac surgery	7.5	Strong recommendation, moderate certainty.
	Hip fracture	8.0	Applies to patients with CAD or other risk factors. Conditional recommendation, moderate certainty.
Frankfurt Consensus Conference 2018 (15)	Acute GI bleed (clinically stable)	7.0 to 8.0	Conditional recommendation, low certainty.
Ottawa expert panel 2018 (16)	Liver resection	7.0 without CAD	Evidence not graded.

Organization	Indication for transfusion	Recommended threshold (†)	Comment
		8.0 with CAD	
British Committee for Standards in Haematology 2017 (17)	Major bleeding	No threshold	Guideline supports restrictive thresholds for GI hemorrhage and trauma, but does not define them.
European Society of Anaesthesiology 2017 (18)	Surgery (with bleeding)	7.0 to 9.0	Strong recommendation, low quality evidence.
American Association of Blood Banks 2016 (19)	Ortho. surgery, cardiac surgery, cardiovascular disease	8.0	Strong recommendation, moderate quality evidence.
	Other inpatients	7.0	Strong recommendation, moderate quality evidence.
National Institute for Health and Clinical Excellence (UK) 2015 (20)	General	7.0	Applies to patients who do not have major bleeding or acute coronary syndrome. Reviewed 2019.
Royal College of Obstetricians and Gynaecologists 2015 (21)	Obstetrics	No threshold	There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be made on clinical and haematological grounds. Reviewed 2018.

†–all thresholds expressed as hemoglobin levels (g/dl)

CAD–coronary artery disease, ELSO–Extracorporeal Life Support Organization

Systematic reviews

Recent systematic reviews of RBC transfusion thresholds are listed in Table 4. Since we are not doing any synthesis of the results of the reviews, we did not appraise their methodological quality. While our protocol specified a three year time period for including systematic reviews, some older reviews were picked up in the search because they mentioned guidelines. We inspected those reviews (22-26) and none of them cited any studies using a hemoglobin threshold below 7.0 g/dl. The review by Shehata (26) (on cardiac surgery patients) had to be excluded because the authors failed to include the evidence table in their published article or supplemental material.

The most comprehensive review of RBC transfusion thresholds is in a Cochrane review published in 2021 (27), with searches completed in November 2020. The review provides a table detailing the transfusion strategies used in experimental and control groups for each included study. We examined those strategies, and found a plurality (17/48 studies, 35%) reporting a restrictive threshold of 7.0, and a majority (34/48 studies, 71%) reporting restrictive thresholds between 7.0 and 8.0 inclusive. Four studies used hematocrit thresholds of 24% or 25% (hematocrit of 24% is considered equivalent to hemoglobin of 8.0 g/dl), and four studies used strategies not based on hemoglobin or hematocrit levels.

One study cited in the Cochrane review used a hemoglobin threshold below 7.0 g/dl (28, 29). This study was analyzed in our previous report on transfusion thresholds in orthopedic surgery. A threshold of 6.4 g/dl (4.0 mmol/l) was used for hip or knee replacement patients younger than 50 years of age and without any risk factors. Intermediate-risk patients were managed with a threshold of 7.2 g/dl and high risk patients were managed with a threshold of 8.9. Patients in all risk groups were pooled so we cannot determine the outcomes for the subgroup of patients managed with the lowest threshold. Other than this study, none of the studies reported in any of

the other systematic reviews in Table 4 used a hemoglobin threshold below 7.0. Approximately half of the cited studies used a threshold of 7.0 as their restrictive threshold, and the rest used thresholds ranging from 7.5 to 9.7.

Another review cited a pilot study from Germany in 2006 (30) that compared patients managed using a hematocrit threshold of 20% (equivalent to hemoglobin of 6.7 g/dl) during coronary artery bypass surgery to patients managed using a hematocrit threshold of 25% (equivalent to 8.3 g/dl hemoglobin). Because the study was so small (54 patients, six transfusions, and only one serious adverse event), it provides little useful information about the safety or effectiveness of the lower threshold.

Table 4. Systematic review findings

Reviewer	Indication for transfusion	N studies	Restrictive threshold	Comment
Carson 2021 (27) (Cochrane review)	Various	48	6.4 to 9.7	See discussion above. The reviewers' meta-analysis on threshold level compared thresholds of 7.0 to 7.5 to thresholds of 8.0 to 9.0.
Trentino 2020 (31)	Review of reviews	19 reviews	7.0 to 9.5	No reviews included studies with a threshold below 7.0.
Barrie 2022 (32)	Spine surgery	6	7.3 to 9.0	
Abbasciano 2021 (33)	ECMO	10	7.0 to 14	Only one study compared thresholds.
Florez-Perdomo 2021 (34)	Traumatic brain injury	4	7.0	All studies used a restrictive threshold of 7.0.
Lenet 2021 (35)	Surgery	14	7.0 to 9.0	No studies used a threshold below 7.0.
Mofor 2021 (36)	Subarachnoid hem.	5	7.0 to 11.1	
W Zhang 2021 (37)	Critical care	7	7.0 to 7.5	No studies used a threshold below 7.0.
Y Zhang 2021 (38)	Acute MI	6	8.0	Three studies used a restrictive threshold of 8.0, three studies used a hematocrit threshold of 24%.
Chekol 2020 (39)	Surgery	4	7.0 to 8.0	No studies used a threshold below 7.0.
Kashani 2020 (40)	Cardiac surgery	10	7.0 to 8.0	Four of the studies used hematocrit thresholds of 20-25%.
Yang 2020 (41)	Cancer	7	7.0	All studies used a restrictive threshold of 7.0.
Yao 2020 (42)	Critical care	8	7.0	Excluded trials with restrictive threshold above 7.0. No trials used a threshold below 7.0.
Chai 2019 (43)	Various	36	7.0 to 9.7	Review did not include a complete evidence table, but none of the cited studies used a threshold below 7.0.
Derzon 2019 (44)	Various	25	7.0 to 10.0	Included interventions other than restrictive thresholds.
Hirano 2019 (45)	Sepsis	3	7.0	All studies used a restrictive threshold of 7.0.
Zhu 2019 (46)	Hip fracture	9	8.0 to 9.7	One trial had a restrictive strategy based on symptoms and not on hemoglobin level.

Unless otherwise noted, transfusion thresholds are reported in g/dl hemoglobin.

Primary studies

While we did not conduct an exhaustive search for clinical trials of RBC transfusion thresholds, we believe our search captured a representative sample of recent studies. Since the purpose of this

report is to identify possible indications for a hemoglobin threshold lower than 7.0 g/dl and not to evaluate the safety and effectiveness of lower thresholds, there is not a substantial risk of bias from this approach.

We found 39 primary studies published since 2020 that reported on RBC transfusion thresholds, and only one included a hemoglobin threshold below 7.0 g/dl. Like the orthopedic surgery study described above, this study (47) included a variety of surgical patients, is also from a hospital in the Netherlands. The focus of the study was on the comparative accuracy of two different hemoglobin measurement techniques. Healthy young patients (specific inclusion criteria were not reported) were managed using a hemoglobin threshold of 6.4 g/dl (4.0 mmol/l). Since the study did not compare a lower threshold to a higher threshold, we cannot draw any conclusions about the safety and effectiveness of the lower threshold.

The TRACE-2 survey (48) reported on transfusion practices among 401 responding critical care physicians. The article reported survey results as medians and quartiles, and did not report maxima and minima, so at best we can put a 25% cap on the number of physicians using a hemoglobin threshold below 7.0 g/dl. There were no patient groups for whom the 25th percentile transfusion threshold was below 7.0, and for most indications, the 25th percentile was at 7.0.

Conclusions

While there is considerable evidence supporting a restrictive transfusion threshold of 7 g/dl in many groups of patients, including surgical patients, cancer patients, and critical care patients, there is very little evidence for or against a hemoglobin threshold below 7 g/dl. No systematic reviews have analyzed evidence for thresholds below 7, and the only guideline recommending a threshold below 7 was for an under-resourced health system in sub-Saharan Africa.

A limited search for recent clinical studies and examination of studies cited in systematic reviews identified two studies where thresholds of 6.4 g/dl (4.0 mmol/l) were used in young patients having surgery. Neither study was designed or reported in a way that would allow us to ascertain whether or not the lower threshold adversely affected patient outcomes.

Methods

Literature Search

Literature searches were completed in February 2022. Review searches were limited to only the most recent three years because we expected that consideration of hemoglobin thresholds below 7.0 g/dl would be a recent phenomenon, and because reviews completed recently would still include studies performed in earlier years. Guideline searches were limited to only the most recent five years. NICE Evidence Search included a large number of potentially-relevant hits since each section of the UK transfusion handbook and each section of the guidelines for managing a transfusion service had separate entries in the NICE database.

Table 5. Guideline search

Database or organization	Keywords or syntax	Hits	Marked for retrieval	Included
ECRI Guidelines Trust	transfusion limit to publication year 2017-22	28	8	3
Guidelines International Network	transfusion limit to publication year 2017-22	3	0	0

Table 6. Evidence clearinghouse search

Search keywords	Evidence type	Hits	Marked for retrieval	Included
NICE Evidence Search (NHS)				
transfusion	Guidance	†-990	46	3
	Systematic reviews	‡-1,802	30	0

†-only the 500 most relevant hits (by NICE algorithm) were screened
‡-only the 300 most relevant hits (by NICE algorithm) were screened

Table 7. MEDLINE search

Search	Syntax	Hits	Retrieved	Included
1	(transfus* adj2 (restrict* or liberal or threshold* or trigger* or criteri* or strateg* or decid* or decis*)).mp.	2,968	—	—
2	(guideline* or guidance).mp. or exp Guideline/ or exp Practice Guideline/	659,971	—	—
3	1 AND 2	647	—	—
4	limit 3 to (english language and yr="2017 -Current")	225	—	—
5	limit 1 to (meta analysis or systematic reviews)	161	—	—
6	limit 5 to (english language and yr="2020 -Current")	34	—	—
7	4 or 6	251	—	—
	exclude 3 duplicate references within set	248	42	20
8	Cochrane optimized filter for clinical trials	1,311,434	—	—
9	1 and 8	597	—	—
10	limit 9 to (english language and yr="2020 -Current")	83	—	—
	exclude 1 duplicate reference within set	82	22	22

mp: keyword (title, abstract, subject heading)

Table 8. Embase search

Search	Syntax	Hits	Retrieved	Included
1	transfus* NEAR/2 (restrict* OR liberal OR threshold* OR criteri* OR strateg* OR decid* OR decis*)	4,628	—	—
2	#1 AND ('practice guideline'/de OR guideline:ti,ab OR guidance:ti,ab)	758	—	—
3	#2 AND [english]/lim AND [2017-2022]/py	377	—	—
4	#1 AND ([systematic review]/lim OR [meta analysis]/lim)	253	—	—
5	#4 AND [english]/lim AND [2020-2022]/py	51	—	—
6	#3 OR #5	423	—	—
7	#6 NOT ('conference abstract'/it OR 'conference paper'/it)	191	—	—
	exclude 1 duplicate reference within set and 138 references duplicating MEDLINE results	52	3	2
8	#1 AND ('clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de)	2,127	—	—
9	#8 AND [english]/lim AND [2020-2022]/py	426	—	—
10	#6 NOT ('conference abstract'/it OR 'conference paper'/it)	217	—	—
	exclude 2 duplicate references within set and 56 references duplicating MEDLINE primary study results	159	22	22

Table 9. Transfusion Evidence Library search

Search	Syntax	Hits	Retrieved	Included
1	threshold* OR trigger* OR restrict*	756	—	—
2	limit to publication years 2020-2022	169	—	—
	exclude 2 duplicate references within set and 21 references duplicating MEDLINE or Embase primary study results	146	3	1

Additional internal reviewers

- Neil Fishman, MD (CMO)
- Jacob T. Gutsche, MD (Critical Care)
- Donald L. Siegel, PhD, MD (Transfusion Medicine)

Conflict of interest disclosures

None of the authors have any relevant financial relationships with commercial interests associated with the subject of this review. The CEP conflict of interest disclosure policy is found on the CEP web site. CEP reports are funded by the University of Pennsylvania Health System.

References

1. Baker L, Park L, Gilbert R, Ahn H, Martel A, Lenet T, et al. Intraoperative red blood cell transfusion decision-making: a systematic review of guidelines. Ann Surg. 2021;274(1):86-96. https://doi.org/10.1097/sla.0000000000004710

2. Norfolk D, ed. Handbook of Transfusion Medicine. Norwich, UK: United Kingdom Blood Services, 2014. https://www.transfusionguidelines.org/transfusion-handbook

3. Moretti K, Marqués CG, Garbern S, Mbanjumucyo G, Uwamahoro C, Beaudoin FL, et al. Transfusion, mortality and hemoglobin level: associations among emergency department patients in Kigali, Rwanda. Afr J Emerg Med. 2020;10(2):68-73. https://doi.org/10.1016/j.afjem.2020.01.004

4. Braxley N, Calderon G. Emergency Medicine Clinical Guidelines. Kirgali, Rwanda: Ministry of Health; 2016. https://www.medbox.org/document/rwanda-emergency-medicine-clinical-guidelines

5. Laine L, Barkun AN, Saltzman JR, Martel M, Leontiadis GI. ACG Clinical Guideline: Upper gastrointestinal and ulcer bleeding. Am J Gastroenterol. 2021;116(5):899-917. https://doi.org/10.14309/ajg.0000000000001245

6. Triantafyllou K, Gkolfakis P, Gralnek IM, Oakland K, Manes G, Radaelli F, et al. Diagnosis and management of acute lower gastrointestinal bleeding: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2021;53(8):850-68. https://doi.org/10.1055/a-1496-8969

7. Vlaar APJ, Dionne JC, de Bruin S, Wijnberge M, Raasveld SJ, van Baarle F, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med. 2021;47(12):1368-92. https://doi.org/10.1007/s00134-021-06531-x

8. Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, et al. STS/SCA/AmSECT/ SABM update to the clinical practice guidelines on patient blood management. Ann Thorac Surg. 2021;112(3):981-1004. https://doi.org/10.1016/j.athoracsur.2021.03.033

9. Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. Intensive Care Med. 2020;46(4):673-96. https://doi.org/10.1007/s00134-019-05884-8

10. Griffiths R, Babu S, Dixon P, Freeman N, Hurford D, Kelleher E, et al. Guideline for the management of hip fractures 2020: guideline by the Association of Anaesthetists. Anaesthesia. 2020;76(2):225-37. https://doi.org/10.1111/anae.15291

11. Singh G, Nahirniak S, Arora R, Legare J, Kanji HD, Nagpal D, et al. Transfusion thresholds for adult respiratory extracorporeal life support: an expert consensus document. Can J Cardiol. 2020;36(9):1550-3. https://doi.org/10.1016/j.cjca.2020.06.014

12. Oakland K, Chadwick G, East JE, Guy R, Humphries A, Jairath V, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. Gut. 2019;68(5):776-789. https://doi.org/10.1136/gutjnl-2018-317807

13. Hallet J, Jayaraman S, Martel G, Ouellet J-B, Lin Y, McCluskey S, et al. Patient blood management for liver resection: consensus statements using Delphi methodology. HPB. 2019; 21(4):393-404. https://doi.org/10.1016/j.hpb.2018.09.022

14. Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascón P, Glaspy J, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv96-iv110. https://doi.org/10.1093/annonc/mdx758

15. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. JAMA. 2019;321(10):983-97. https://doi.org/10.1001/jama.2019.0554

16. Bennett S, Tinmouth A, McIsaac DI, English S, Hébert PC, Karanicolas PJ, et al. Ottawa criteria for appropriate transfusions in hepatectomy: using the RAND/UCLA appropriateness method. Ann Surg. 2018;267(4). https://doi.org/10.1097/sla.0000000000002205

17. Hunt BJ, Allard S, Keeling D, Norfolk D, Stanworth SJ, Pendry K; British Committee for Standards in Haematology. A practical guideline for the haematological management of major haemorrhage. Br J Haematol. 2015;170(6):788-803. https://doi.org/10.1111/bjh.13580

18. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol. 2017;34(6):332-95. https://doi.org/10.1097/eja.0000000000000630

19. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016; 316(19):2025-35. https://doi.org/10.1001/jama.2016.9185

20. Blood transfusion: NICE Guideline (NG24). London: National Institute for Health and Care Excellence. 2015. https://www.nice.org.uk/guidance/ng24

21. Blood transfusions in obstetrics (RCOG Green-top Guideline No. 47). London: Royal College of Obstetricians and Gynaecologists. 2015. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-47.pdf

22. Gu W, Gu X, Wu X, Chen H, Kwong JSW, Zhou L, et al. Restrictive versus liberal strategy for red blood-cell transfusion: a systematic review and meta-analysis in orthopaedic patients. J Bone Joint Surg Am. 2018;100(8):686-95. https://doi.org/10.2106/jbjs.17.00375

23. Simon GI, Craswell A, Thom O, Fung YL. Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials: a systematic review and meta-

analysis. Lancet Haematol. 2017;4(10):e465-74. https://doi.org/10.1016/s2352-3026(17)30141-2

24. Franchini M, Marano G, Mengoli C, Pupella S, Vaglio S, Munoz M, et al. Red blood cell transfusion policy: a critical literature review. Blood Transfus. 2017;15(4):307-17. https://doi.org/10.2450/2017.0059-17
25. Hoeks MPA, Kranenburg FJ, Middelburg RA, van Kraaij M, Zwaginga J. Impact of red blood cell transfusion strategies in haemato-oncological patients: a systematic review and meta-analysis. Br J Haematol. 2017;178(1):137-51. https://doi.org/10.1111/bjh.14641
26. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. Crit Care. 2018;22(1):142. https://doi.org/10.1186/s13054-018-2062-5
27. Carson JL, Stanworth SJ, Dennis JA, Trivella M, Roubinian N, Fergusson DA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev. 2021;12:CD002042. https://doi.org/10.1002/14651858.cd002042.pub5
28. So-Osman C, Nelissen R, Te Slaa R, Coene L, Brand R, Brand A. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. Vox Sang. 2009;98(1):56-64. https://doi.org/10.1111/j.1423-0410.2009.01225.x
29. So-Osman C, Nelissen R, Brand R, Faber F, Slaa RT, Stiggelbout A, et al. The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study. Blood transfusion 2013;11(2):289-95. https://doi.org/10.2450/2013.0172-12
30. von Heymann C, Sander M, Foer A, Heinemann A, Spiess B, Braun J, et al. The impact of an hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft surgery on oxygen delivery and clinical outcome – a randomized controlled study. Critical Care. 2006;10(2):R58. https://doi.org/10.1186/cc4891
31. Trentino KM, Farmer SL, Leahy MF, Sanfilippo FM, Isbister JP, Mayberry R, et al. Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: an overview of systematic reviews. BMC Med. 2020;18(1): 154. https://doi.org/10.1186/s12916-020-01614-w
32. Barrie U, Youssef CA, Pernik MN, Adeyemo E, Elguindy M, Johnson ZD, et al. Transfusion guidelines in adult spine surgery: a systematic review and critical summary of currently available evidence. Spine J. 2022;22(2):238-48. https://doi.org/10.1016/j.spinee.2021.07.018
33. Abbasciano RG, Yusuff H, Vlaar APJ, Lai F, Murphy GJ. Blood transfusion threshold in patients receiving extracorporeal membrane oxygenation support for cardiac and respiratory failure-a systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2021;35(4): 1192-1202. https://doi.org/10.1053/j.jvca.2020.08.068
34. Florez-Perdomo W, Garcia-Ballestas E, Martinez-Perez R, Agrawal A, Deora H, Joaquim AF, et al. Hemoglobin levels as a transfusion criterion in moderate to severe traumatic brain injury: a systematic review and meta-analysis. Br J Neurosurg. 2021 Jun 21:1-7. https://doi.org/10.1080/02688697.2021.1940850

35. Lenet T, Baker L, Park L, Vered M, Zahrai A, Shorr R, et al. A systematic review and meta-analysis of randomized controlled trials comparing intraoperative red blood cell transfusion strategies. Ann Surg. 2022; 275(3):456-466. https://doi.org/10.1097/sla.0000000000004931

36. Mofor P, Oduguwa E, Tao J, Barrie U, Kenfack YJ, Montgomery E, et al. Postoperative transfusion guidelines in aneurysmal cerebral subarachnoid hemorrhage: a systematic review and critical summary of available evidence. World Neurosurg. 2022;158:234-243e5. https://doi.org/10.1016/j.wneu.2021.12.007

37. Zhang W, Zheng Y, Yu K, Gu J. Liberal transfusion versus restrictive transfusion and outcomes in critically ill adults: a meta-analysis. Transfus Med Hemotherapy. 2021;48(1):60-8. https://doi.org/10.1159/000506751

38. Zhang Y, Xu Z, Huang Y, Ye Q, Xie N, Zeng L, et al. Restrictive vs. liberal red blood cell transfusion strategy in patients with acute myocardial infarction and anemia: a systematic review and meta-analysis. Front Cardiovasc Med. 2021;8:736163. https://doi.org/10.3389/fcvm.2021.736163

39. Chekol WB, Teshome M, Nigatu YA, Melesse DY. Hemoglobin threshold and clinical predictors for perioperative blood transfusion in elective surgery: systemic review. Trends Anaesth Crit Care. 2020;31:8-15. https://doi.org/10.1016/j.tacc.2019.12.003

40. Kashani HH, Lodewyks C, Kavosh MS, Jeyaraman MM, Neilson C, Okoli G, et al. The effect of restrictive versus liberal transfusion strategies on longer-term outcomes after cardiac surgery: a systematic review and meta-analysis with trial sequential analysis. Can J Anaesth. 2020;67(5):577-87. https://doi.org/10.1007/s12630-020-01592-w

41. Yang X, Dai X, Liu C, Lu J, Lin S. Restrictive versus liberal transfusion strategies in patients with malignant neoplasm-a meta-analysis of randomized controlled trials. Transfus Apheresis Sci. 2020;59(5):102825. https://doi.org/10.1016/j.transci.2020.102825

42. Yao R, Ren C, Zhang Z, Zhu Y, Xia Z, Yao Y. Is haemoglobin below 7.0 g/dL an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review. BMJ Open. 2020;10(2):e030854. https://doi.org/10.1136/bmjopen-2019-030854

43. Chai KL, Cole-Sinclair M. Review of available evidence supporting different transfusion thresholds in different patient groups with anemia. Ann NY Acad Sci. 2020;1450(1):221-38. https://doi.org/10.1111/nyas.14203

44. Derzon JH, Clarke N, Alford A, Gross I, Shander A, Thurer R. Restrictive transfusion strategy and clinical decision support practices for reducing RBC transfusion overuse. Am J Clin Pathol. 2019;152(5):544-57. https://doi.org/10.1093/ajcp/aqz070

45. Hirano Y, Miyoshi Y, Kondo Y, Okamoto K, Tanaka H. Liberal versus restrictive red blood cell transfusion strategy in sepsis or septic shock: a systematic review and meta-analysis of randomized trials. Crit Care. 2019 July 25. https://doi.org/10.1186/s13054-019-2543-1

46. Zhu C, Yin J, Wang B, Xue Q, Gao S, Xing L, et al. Restrictive versus liberal strategy for red blood-cell transfusion in hip fracture patients: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98(32):e16795. https://doi.org/10.1097/md.0000000000016795

47. Spronk A, De Jong R, Koopman S, Hoeks S, Stolker RJ. Blood transfusion decisions cannot be based on percutaneous haemoglobin measurements. Anest Intens Ther. 2021;53(2):103-7. https://doi.org/10.5114/ait.2021.105658

48. de Bruin S, Eggermont D, van Bruggen R, de Korte D, Scheeren TWL, Bakker J, et al. Transfusion practice in the bleeding critically ill: an international online survey—the TRACE-2 survey. Transfusion. 2021. https://doi.org/10.1186/s13054-019-2591-6