

Guidelines for the use of red blood cell products based on scientific evidence (Revised
2nd edition)

Yuji Yonemura¹⁾¹³⁾, Masanori Matsumoto²⁾¹³⁾, Eiichi Inada³⁾¹³⁾, Yasunori Ueda⁴⁾¹³⁾,
Kohshi Ohishi⁵⁾¹³⁾, Takahiko Kubo⁶⁾¹³⁾, Midori Kumakawa⁷⁾¹³⁾, Eizaburo Sueoka⁸⁾¹³⁾,
Takashi Sonoki⁹⁾¹³⁾, Kazuhiro Nagai¹⁰⁾¹³⁾, Naohito Fujishima¹¹⁾¹³⁾, Tadashi
Matsushita¹²⁾¹³⁾

- 1) Department of Transfusion Medicine and Cell Therapy, Kumamoto University
Hospital
- 2) Department of Transfusion Medicine, Nara Medical University
- 3) Department of Anesthesiology and Pain Medicine, Juntendo University Faculty of
Medicine
- 4) Department of Hematology/Oncology, Kurashiki Central Hospital
- 5) Transfusion Medicine and Cell Therapy, Mie University Hospital
- 6) Shirota Obstetrical and Gynecological Hospital
- 7) Division of Transfusion Medicine, Fukuoka University Hospital
- 8) Clinical Laboratory, Saga Medical University
- 9) Department of Hematology/Oncology, Wakayama Medical University
- 10) Transfusion and Cell Therapy Unit, Nagasaki University Hospital
- 11) Division of Blood Transfusion, Akita University Hospital
- 12) Department of Transfusion Service, Nagoya University Hospital
- 13) Guideline Committee of the Japan Society of Transfusion Medicine and Cell
Therapy.

Task Force Committee on Guidelines for the Use of Red Blood Cell Products

Key Words: red blood cell transfusion, autologous blood transfusion, transfusion trigger, guideline

目次

1. Introduction
2. Types of red blood cell products and evaluation of their administration
3. Guidelines for red blood cell products
 - 1) Trigger values and recommendations for the use of red blood cell products in various disorders
 - CQ1-1 What are the red blood cell transfusion triggers for anemia due to aplastic anemia, myelodysplastic syndrome, etc.?
 - CQ1-2 What are the red blood cell transfusion triggers for anemia due to chemotherapy for solid cancers, etc.?
 - CQ1-3 What are the red blood cell transfusion triggers for anemia in chemotherapy for hematopoietic tumors and hematopoietic stem cell transplantation?
 - CQ1-4 What is the red blood cell transfusion trigger for anemia that is clearly treatable by replacement therapy such as iron-deficiency and vitamin B12-deficiency anemia?
 - CQ1-5 What is the red blood cell transfusion trigger for autoimmune hemolytic anemia?
 - CQ1-6 What is the red blood cell transfusion trigger for acute anemia due to gastrointestinal bleeding?
 - CQ1-7 What is the red blood cell transfusion trigger for perioperative anemia?
 - CQ1-8 What is the red blood cell transfusion trigger for anemia in non-cardiac surgery of patients with heart disease, particularly, ischemic heart disease?
 - CQ1-9 What is the red blood cell transfusion trigger for anemia due to renal failure?
 - CQ1-10 What is the red blood cell transfusion trigger for anemia due to surgery using an artificial heart-lung machine?
 - CQ1-11 What is the red blood cell transfusion trigger for anemia in severely ill or septicemic patients?
 - 2) Does the storage duration of red blood cell products have any clinical effects?
 - 3) Indications and recommendations of autologous blood donation in various disorders
 - CQ2-1 Is there an indication for autologous blood transfusion in orthopedic surgery (knee replacement, hip replacement, scoliosis surgery, etc.)?
 - CQ2-2 Is there an indication for autologous blood transfusion in gynecological surgery (surgery for uterine myoma, uterine cancer, etc.)?
 - CQ2-3 What are indications for autologous blood transfusion in obstetric surgery and the volume of predeposited blood?
 - CQ2-4 Can autologous blood transfusion be recommended in cardiovascular surgery (open-heart surgery, etc.)?
 - CQ2-5 Can autologous blood transfusion be recommended in surgeries that involve bleeding such as colectomy and hepatectomy?

1. Introduction

1) Objectives for the preparation of these guidelines

Transfusion is supportive therapy in perioperative medical care and management of blood diseases, but its risks and benefits must be weighed in every case. Patient blood management (PBM) is increasingly invoked around the world as a preferred practice, and autologous blood transfusion persists, especially in Japan, as a countermeasure to adverse immunological reactions and residual infection risks associated with allogeneic transfusion. Moreover, demographic changes that threaten the sufficiency of our blood supply call for ongoing development of techniques and methods in autologous blood transfusion. Allogeneic blood, even from altruistic volunteer donors, is not 100% safe. Therefore, we as healthcare professionals are obligated to be conscientious stewards of donated blood. To this end, clinicians must avoid unnecessary use of blood products and promote evidence-based safe and appropriate transfusion.

The Guidelines for the Use of Blood Products, initially called “Rules for the Appropriate Use of Blood Products,” were compiled in 1986, enacted by the Ministry of Health and Welfare, and supplemented with criteria for the use of platelets in 1994. Guidelines concerning the implementation were named the 1989 “Guidelines for Appropriate Transfusion Therapy,” and the Ministry of Health, Labour and Welfare established the “Guidelines for the Use of Blood Products” and “Guidelines for the Implementation of Transfusion Therapy” in 1999. Thereafter, these guidelines have been

revised several times with the most recent partial revision in 2016. Thusfar, recommendation levels have not been set based on evidence. Recently, many papers arguing that liberal transfusion is not more beneficial to patients than restrictive transfusion have appeared. The present red blood cell product guidelines were prepared primarily by the Japan Society of Transfusion Medicine and Cell Therapy. They are intended to support healthcare professionals in making appropriate judgments concerning the use of red blood cell products, promote the appropriate use of red blood cell products, and improve therapy. The present guidelines were prepared on the basis of scientific grounds, but they only show evidence of the results of clinical studies and do not presume to be applicable in all cases. In chronic anemia, it is permitted to set a transfusion trigger higher than suggested if the patient has severe subjective symptoms. In clinical situations, it is necessary that the use of red blood cell products be guided by the sound judgment of healthcare professionals, and the guidelines do not restrict this. Thus, no legal liability is assumed by anyone providing care or by guideline authors, sponsors, publishers, etc., for adhering, or not, to these guidelines.

2) Circumstances of the guidelines preparation

This project was started in 2013 by the Taskforce Concerning the Preparation of the Guidelines for the Use of Red Blood Cell Products, which is a subcommittee of the Guideline Committee of the Japan Society of Transfusion Medicine and Cell Therapy, and was continued as the Study Concerning the Preparation of Transfusion Guidelines based on Scientific

Evidence, subsidized by Health and Labour Sciences Research Grants in March 2014. Members of the Taskforce Concerning the Preparation of Guidelines for the Use of Red Blood Cell Products were selected by the Board of Executives in May 2013, based on their expertise.

For the preparation of the first edition, clinical questions (CQs) were set, the quality of evidence (references) and the “outcome: usefulness concerning the CQ in question” were evaluated, and recommendation grades were determined, over a period of 3 years. The guidelines were prepared, in principle, by a standard method widely adopted in Japan (Minds2014), and the first edition was published as the “Guidelines for the Use of Red Blood Cell Products based on Scientific Evidence” in the Journal of the Japan Society of Transfusion Medicine and Cell Therapy in December 2016.¹⁾ The final report of the “Study Concerning the Preparation of Transfusion Guidelines based on Scientific Evidence” was made in March 2016, and, according to the results of the series of operations, the Ministry of Health, Labour and Welfare entirely revised the “Guideline for the Use of Blood Products” in March 2017.

The advances of modern clinical medicine have been remarkable, and, for the appropriate use of blood products based on the latest knowledge in Japan, it is necessary to update the guidelines by continuously carrying out the cycle of collection of evidence→evaluation→integration→ recommendation. Although the first edition included papers published by 2014, more papers have recently been reported, and the Guideline Committee of the Japan

Society of Transfusion Medicine and Cell Therapy decided to revise the first edition by incorporating papers that appeared through 2017. Simultaneously with this revision, the AMED Research and Development Project, “Study Concerning the Use of Blood Products and Implementation of Transfusion Therapy for more Appropriate Application” was started. In the revised edition, new data that became available after 2015 were incorporated, and the evidence as a whole was reconstituted and reevaluated, to further improve the guidelines.

3) Preparation Committee members

- Project subsidized by Health and Labour Sciences Research Grants

Study Concerning the Preparation of Transfusion Guidelines based on Scientific Evidence

Research Representative:

Tadashi Matsushita, Nagoya University

Disclosure of COI: Commissioned research funds (Chugai Pharmaceutical Co., Ltd.), scholarship donations (Novo Nordisk Pharma Ltd. and Kaketsuken), lecture fees (Shire, Novo Nordisk Pharma Ltd., and Bioverativ)

- Guideline Committee of the Japan Society of Transfusion Medicine and Cell Therapy.

Executive board member in charge:

Masanori Matsumoto, Nara Medical University

Disclosure of COI: Donations (Chugai Pharmaceutical Co., Ltd., Asahi Kasei Pharma Corporation, and Bayer Yakuhin, Ltd.), lecture fees (Alexion and Asahi Kasei Pharma Corporation)

Task Force Committee for the preparation of guidelines for the use of red blood cell products

Committee Chairperson:

Yuji Yonemura, Kumamoto University

Disclosure of COI: Commissioned research fund (Alexion)

Committee Members:

Eiichi Inada, Juntendo University

Disclosure of COI: Lecture fees (Japan Blood Products Organization)

Yasunori Ueda, Kurashiki Central Hospital

Disclosure of COI: None

Kohshi Ohishi, Mie University

Disclosure of COI: Scholarship donations (Kyowa Hakko Kirin Co., Ltd. and Astellas Pharma Inc.) Lecture fees (Chugai Pharmaceutical Co., Ltd.)

Takahiko Kubo, Shirota Obstetrical and Gynecological Hospital

Disclosure of COI: None

Midori Kumakawa, Fukuoka University

Disclosure of COI: None

Eizaburo Sueoka, Saga University

Disclosure of COI: None

Takashi Sonoki, Wakayama Medical University

Disclosure of COI: Scholarship donations (Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Inc., and Mochida Pharmaceutical Co., Ltd.)

Kazuhiro Nagai, Nagasaki University

Disclosure of COI: Other rewards (fees for examination of health insurance claims) (Nagasaki National Health Insurance Organizations)

Naohito Fujishima, Akita University

Disclosure of COI: Lecture fees (Pfizer Japan Inc.)

4) Preparation methods

● Setting of clinical questions (CQs)

Clinical questions (CQs) were set concerning 5 diseases in which autologous blood transfusion is considered to be performed frequently at present, because specific disease names are not shown concerning the 11 conditions included in the indications mentioned in Chapter 2, “Appropriate Use of Red Blood Cell Concentrates” of the “Guidelines for the Use of Blood Products” (trigger values in pregnant women were excluded in the present guidelines, because the trigger varies with the cause of anemia) and the indications mentioned in Chapter 11, “Autologous Blood Transfusion” of the “Guidelines for Implementation of Transfusion Therapy.” Also, as many papers that evaluated whether the difference in the storage period of red blood cell products affects the prognosis have been published, they are added in the present 2nd edition. As shown below, as a result of screening of 9,345 papers from Japan and abroad concerning red blood cell transfusion that appeared over 1995-2014, 978 were adopted by primary selection. Other important literature and papers necessary for the preparation of

statements were added as hand-searched references, and overall evaluation was eventually made concerning 188 papers, to prepare the first edition of the guideline. In the present revision, 288 papers were adopted by primary selection using the same procedure. Concerning other important literature and papers necessary for the preparation of statements, 12 hand-searched papers were added, and overall evaluation was made concerning 125 papers, excluding the 188 papers adopted by the first edition, to prepare the 2nd edition of the guideline. The evidence level and recommendation grade for each CQ were determined according to the “Minds Handbook for Clinical Practice Guideline Development 2014.”²⁾ In the present guidelines, Preparation Committee members were assigned to each CQ, and the chairperson was appointed for the management of the entire project.

- Search of databases

For exhaustive searches, 3 databases, i.e., PubMed, the Cochrane Library, and Ichushi-Web were considered essential. As for MEDLINE, PubMed was used in consideration of the cost.

- Establishment of literature searching formulas

For each CQ, a searching formula was prepared by combining keywords and thesauri (MeSH, etc.) with cooperation by experts in medical literature searching at the International Medical Information Center (IMIC).

- Screening and literature management

- (1) Primary screening

Screening was performed using predetermined literature selection and exclusion criteria. In primary screening, papers that did not match the CQ were excluded according to the title and abstract. Those that were difficult to judge were retained, in principle. From these papers, a data set for secondary screening was prepared, and the texts of the literature were collected.

- Details of literature retrieval

Source	Year of beginning of search	Number of hits by search	Number of papers adopted by primary selection
PubMed	1995	3,008	647
Cochrane	1995	3,431	219
Ichushi	1995	2,906	112

In the first edition, important papers were presented among those retrieved for each CQ. Draft proposals were prepared and modified through reviews in the taskforce.

Field of search	Literature retrieval			Primary selection			Secondary selection • evaluation of each paper			Addition by hand search	Overall evaluation of evidence		
	PubMed	Cochrane	Ichushi	Papers reviewed	Adopted	Excluded	Papers reviewed	Adopted	Excluded		Papers evaluated	Edition	
												Revised	1st
Red blood cells	401	1,113	293	1,510※	280	1,230	289	113	176	12	313	125	188
Storage period of red blood cell products				1,190*	8	1,182							

※ Includes new CQs set in and after 2015

*Papers subjected to secondary selection for the 1st edition after 2014

(2) Literature management

The literature was electronically retrieved, managed in an integrated fashion, and shared.

(3) Secondary screening

The selection criteria were:

1. Existing clinical practice guidelines
2. Systematic reviews (SRs)
3. Randomized controlled trials (RCTs)
4. Observational studies of a relatively large number of cases

Next, they were classified according to CQs, categorized according to PICO (P: patients, problem, population, I: interventions, C: comparisons, controls, comparators, O: outcomes), bias risk, etc., were simultaneously evaluated, and listed as a table for the evaluation of evidence as a whole.

● Evidence as a whole and its summary

Evidence as a whole was prepared concerning each outcome, and the evidence as a whole integrating the bias risk, non-directness, inconsistency, inaccuracy, evaluation of publication (report) bias, magnitude of the intervention effect, dose-response curve, and possibility of attenuation of the effect by confounding factors (evaluation of the evaluation when observational studies are included in the evidence as a whole) was compiled.

The strength of recommendation is indicated at 2 levels: [1] strongly recommended or [2] weakly recommended. The strength of recommendation is shown with the strength of evidence of the overall outcome (A, B, C, D).

A (strong): There is strong confidence in the estimate of the effect

B (moderate): There is moderate confidence in the estimate of the effect

C (weak): The confidence in the estimate of the effect is limited

D (very weak): There is little confidence in the estimate of the effect

5) Publication and revision

The present guidelines are published in the journal of the Japan Society of Transfusion Medicine and Cell Therapy and posted on its web site. They will also be revised with the accumulation of scientific evidence.

6) Funding and conflicts of interest

Funds for the preparation of the present guidelines were obtained from a Health and Labour Sciences Research Grant for the “Study Concerning the Preparation of Transfusion Guidelines Based on Scientific Evidence”. The contents of the present guidelines are not beholden to particular profitable or non-profitable organizations, drugs, or medical equipment firms. The preparation committee has disclosed potential conflicts of interest to the Japan Society of Transfusion Medicine and Cell Therapy.

2. Types of red blood cell products and evaluation of their administration

The Japanese Red Cross Society initiated pre-storage leukocyte reduction in January 2007 and has provided leukocyte-reduced red blood cell concentrates (Red Blood Cells,

Leukocytes Reduced (RBC-LR), NISSEKI and Irradiated Red Blood Cells, Leukocytes Reduced (Ir-RBC-LR), NISSEKI) since August 2014. RBC-LR NISSEKI is prepared by mixing 28 or 56 mL of a blood preservation solution (CPD solution) with 200 or 400 mL of human blood, removing white blood cells by filtration using a leukocyte reduction filter incorporated in the blood bag set, and mixing the nearly plasma-free red blood cell layer with about 46 or 92 mL of a blood cell preservation solution (MAP solution), with a small amount of residual CPD solution. Ir-RBC-LR NISSEKI is prepared by irradiating RBC-LR NISSEKI. RBC-LR NISSEKI and Ir-RBC-LR NISSEKI have nominal volumes of 140 mL/bag from 200 mL of whole blood (RBC-LR-1) or 280 mL/bag from 400 mL of whole blood (RBC-LR-2). The number of residual leukocytes in the products is specified as $\leq 1 \times 10^6$ /bag, Hct is about 50-55% in the products prepared from 400 mL of whole blood, and the hemoglobin content (Hb) is about 20 g/dL. RBC-LR NISSEKI and Ir-RBC-LR NISSEKI are stored at 2-6°C. The Japan Red Cross Society made the shelf-life 42 days when it obtained approval for manufacturing of MAP-spiked red blood cell concentrates (RBC-M.A.P. NISSEKI), but the shelf-life was reduced to 21 days, owing to the possibility of Yersinia contamination.

The increment of patient Hb concentration by the administration of a red blood cell concentrate can be calculated by the following equation.

Expected increase in Hb (g/dL)

=Amount of administered Hb (g)/Circulating blood volume (dL)

Circulating blood volume (dL)

=70 mL/kg (circulating blood volume/kg of body weight)×body weight (kg)/100

For example, in an adult weighing 50 kg (circulating blood volume: 35 dL), Hb is increased by about 1.5 g/dL by transfusion of 2 units of blood with an Hb of 19 g/dL

(since the volume of RBC-LR NISSEKI prepared from 400 mL of blood is about 280 mL, the amount of Hb contained in 1 bag is about $19 \text{ g/dL} \times 280 / 100 \text{ dL} =$ about 53g).

3. Guidelines for red blood cell products

1) Trigger values and recommendations for the use of red blood cell products for various disorders

CQ1-1 What are the red blood cell transfusion triggers for anemia due to aplastic anemia, myelodysplastic syndrome, etc.?

● Recommendation

In patients with anemia due to aplastic anemia, myelodysplastic syndrome, etc., transfusion is rarely necessary if Hb is $\geq 8 \text{ g/dL}$. The trigger for red blood cell transfusion is recommended to be set at a Hb of $\leq 6-7 \text{ g/dL}$, depending on the patient's condition (2D). If there are complications such as impaired oxygenation, the trigger is permitted to be set higher than the indicated level, and transfusion is recommended even at a Hb of $\geq 7 \text{ g/dL}$ if the patient has severe subjective symptoms (2D).

● Comment

There are no reports that transfusion volume is reduced by lowering the Hb trigger for red blood cell transfusion in patients with hematopoietic disorders. The survival rate is likely to be improved by reducing the transfusion volume. Since transfusion is performed mostly at a Hb of $\geq 6-7 \text{ g/dL}$ before the appearance of anemic symptoms and is so recommended by many guidelines,³⁻⁵⁾ the usefulness of this red blood cell transfusion trigger cannot be evaluated. There has also been no report of adverse events. However, the management of organ impairment associated with iron overload due to transfusion is important, and iron chelating drugs are useful for this purpose.⁶⁾ In addition, erythropoiesis-stimulating agents (ESA) have been shown to be effective in patients with low-risk myelodysplastic syndrome in whom the blood erythropoietin

concentration is ≤ 500 mIU,⁷⁾ and the use of ESA at the point when transfusion begins to be considered may lead to a decrease in the transfusion volume.

CQ1-2 What are the red blood cell transfusion triggers for anemia due to chemotherapy for solid cancers, etc.?

● Recommendation

A Hb of 7-8 g/dL is recommended as a red blood cell transfusion trigger for anemia due to chemotherapy for solid cancers (2D). If there are complications, such as impaired oxygenation, the trigger is allowed to be set higher than the indicated value, and transfusion is recommended even at Hb ≥ 7 g/dL if the patient has severe subjective symptoms (2C).

● Comment

There have been few reports that compared the indications for red blood cell transfusion in chemotherapy for solid cancers. This is considered to be due partly to the tendency to avoid chemotherapy for solid cancer that causes bone-marrow suppression so severe as to require red blood cell transfusion. The survival rate has been shown to be low in groups that underwent transfusion in the perioperative period by meta-analyses in lung cancer⁸⁾ and colon cancer⁹⁾ patients and observational studies of 220 patients with adenocarcinoma of the pancreatic duct,¹⁰⁾ 235 esophageal cancer patients,¹¹⁾ and 520 head and neck cancer patients.¹²⁾ On the other hand, red blood cell transfusion was reported not to be related to recurrence or death by an observational study of 587 ovarian cancer patients.¹³⁾ For this CQ, the recommendation was prepared by referring to red blood cell transfusion in chemotherapy for hematopoietic tumors. The presence or absence of anemic symptoms and complications should be considered in the evaluation of the indications and trigger values for red blood cell transfusion.¹⁴⁾

CQ1-3 What are the red blood cell transfusion triggers for anemia in chemotherapy for hematopoietic tumors and hematopoietic stem cell transplantation?

● Recommendation

Hb of 7-8 g/dL is recommended as a red blood cell transfusion trigger for anemia due to chemotherapy for hematopoietic tumors, hematopoietic stem cell transplantation, etc. (1C).

● Comment

In meta-analysis and SR comparing restrictive transfusion with a red blood cell transfusion trigger up to a Hb of 7 g/dL and liberal transfusion, no significant difference was observed in the mortality rate or transfusion volume.^{15,16)} While there are no reports of direct comparison, it appears unnecessary to distinguish the red blood cell transfusion trigger in chemotherapy for hematopoietic tumors and hematopoietic stem cell transplantation from those for other disorders. There is a report that a prospective study to compare the outcome between triggers of Hb 7 and 12 g/dL in children was discontinued due to the frequent occurrence of hepatic venous occlusion in the latter group.¹⁷⁾ A markedly high trigger may be harmful.

CQ1-4 What is the red blood cell transfusion trigger for anemia that is clearly treatable by replacement therapy such as iron-deficiency and vitamin B12-deficiency anemia?

● Recommendation

Red blood cell transfusion is not recommended for patients with anemia that is clearly treatable by replacement therapy such as iron-deficiency and vitamin B12-deficiency anemia unless it may otherwise be difficult to sustain life (2C).

● Comment

There is no directly related report, and the evidence is weak, but anemia due to iron or vitamin B12 deficiency anemia does not progress markedly in a short period, and reticulocytes can be increased in iron-deficiency anemia by the administration of an iron preparation for about 7 days and in vitamin B12-deficiency anemia in 2-3 days by the administration of vitamin B12. Since they can be consistently treated by replacement therapy, patients should be appropriately rested, and the deficient factor should be supplemented until recovery. Red blood cell transfusion is not recommended unless it may otherwise be difficult to sustain life. This can be surmised from basic indications for red blood cell transfusion products for treatable anemia.

CQ1-5 What is the red blood cell transfusion trigger for autoimmune hemolytic anemia?

● Recommendation

In patients with possibly life-threatening autoimmune hemolytic anemia, it is recommended to perform red blood cell transfusion by selecting blood products that do not produce alloantibodies that induce strong transfusion reactions (2C).

● Comment

In rapidly progressing autoimmune hemolytic anemia that may be life-threatening, red blood cell transfusion should be performed without hesitation in conjunction with any other appropriate therapy. The blood to be used should be selected with due consideration to the presence or absence of alloantibodies and the specificity of autoantibodies. Concerning pre-transfusion testing, guidelines are presented by the Japanese Society of Transfusion Medicine and Cell Therapy.¹⁸⁾ There is a report proposing a Hb of 4-6 g/dL in the context of impaired oxygenation.¹⁹⁾ There is also a report, although it is a retrospective study, that the effectiveness of red blood cell transfusion was similar in 161

patients with autoimmune hemolytic anemia including 124 with warm antibodies alone compared with anemic patients with no autoantibodies, and that the Hb value increased to a similar degree.²⁰⁾ It is even safer if blood products match the patient's Rh(DCEce) and Kidd blood types, incompatibility of which causes severe transfusion reactions.

CQ1-6 What is the red blood cell transfusion trigger for acute anemia due to gastrointestinal bleeding?

● Recommendation

Hb of 7-8 g/dL is recommended as a red blood cell transfusion trigger value for acute anemia due to gastrointestinal bleeding. Transfusion is rarely necessary at Hb \geq 9 g/dL except in special cases (1A).

● Comment

Concerning analysis of the outcome and adverse transfusion reactions after restrictive (Hb: <7.0-8.0 g/dL) and liberal (Hb: <9.0-10.0 g/dL) transfusions in acute upper gastrointestinal bleeding with stable circulatory dynamics, multiple randomized controlled trials (RCTs) and systematic reviews (SRs) have reported the superiority of restrictive transfusion with a transfusion trigger of 7 g/dL with regard to the mortality rate, re-bleeding rate, and incidence of acute coronary artery disease during hospitalization, incidences of pulmonary edema and infection, etc., with a decrease in transfusion volume.²¹⁻²⁴⁾

CQ1-7 What is the red blood cell transfusion trigger value for perioperative anemia?

● Recommendation

Hb of 7-8 g/dL is recommended as a red blood cell transfusion trigger for perioperative anemia unless the patient is elderly or has coronary artery disease (1A).

● Comment

Red blood cell transfusion for perioperative anemia contributes to the recovery of the patient's general condition from intraoperative hemorrhage and postoperative anemia by enhancing tissue oxygen supply. However, in postoperative patients and severely ill patients, correlation of red blood cell transfusion with mortality rates and postoperative complications have been suggested by a number of observational studies and SRs (see the comment for CQ1-2).

There have been comparative evaluations of triggers in restrictive vs. liberal transfusion in perioperative patients with normal volume circulation dynamics and severely ill patients in the ICU. The results of such RCTs and meta-analyses have shown that restrictive transfusion with a trigger Hb of 7-8 g/dL could significantly reduce the transfusion volume compared to liberal transfusion with a higher trigger value^{21,25)} and that there was no significant difference between the two groups in primary endpoints, including the mortality rate 30 days after hospitalization, but the hospital mortality rate was significantly lower in the restrictive transfusion group. In addition, no significant increase was observed in risks such as prolongation of the duration of hospitalization, cardiovascular events, pulmonary edema, cerebrovascular disorders, and severe infections such as pneumonia.^{21,25-28)} Also, the FOCUS study of patients who underwent hip surgery showed no significant difference in the 3-year survival rate or the incidence of complications between the two groups.²⁹⁾

Therefore, setting a restrictive trigger for red blood cell transfusion is considered to be useful for reducing the risk of transfusion in perioperative patients during cardiovascular dynamic management. However, unlike subjects of clinical studies, there are times when more careful evaluation of indications is necessary in individual patients with a wide

variety of clinical conditions.^{21,30)} Particularly, evidence concerning patients with coronary artery disease or cardiovascular complications, surgical patients such as those undergoing tumor surgery and neurosurgery, and elderly patients, who are likely to have a wide variety of complications, is insufficient. Recently, there have been studies that set a restrictive trigger Hb of 8 g/dL for surgical patients and suggested its non-inferiority compared with a liberal transfusion group and guidelines that recommend such a trigger value.²³⁾ This recommendation was made in consideration of the effects of surgical insult and any biological reserve against it in patients with coronary artery disease, and very old patients. Presently, the results of large scale RCTs targeted specifically to such subjects are also meager.

CQ1-8 What is the red blood cell transfusion trigger for anemia in non-cardiac surgery of patients with heart disease, particularly, ischemic heart disease?

● Recommendation

A red blood cell transfusion trigger of 8-10 g/dL is recommended for anemia in non-cardiac surgery of patients with heart disease, particularly, ischemic heart disease (2C).

● Comment

Various observational studies have been conducted concerning red blood cell transfusion in patients with heart disease, particularly, ischemic heart disease. The views about the correlation between transfusion and mortality risk vary among reports as they are affected by study design and bias. It is necessary to evaluate the red blood cell transfusion trigger value in the perioperative period of non-cardiac surgery in such patients as a cohort different from patients without ischemic heart disease because of the importance of cardiac function as a compensation mechanism for anemia.

Typical of RCTs, there are sub-group analyses in the TRICC study by Hebert et al.^{26,31)}

As a result, no difference was observed in the trigger of blood Hb concentration, mortality rate, duration of hospitalization, multiple organ failure score, etc., between restrictive and liberal transfusion groups. On the other hand, the mortality rate was suggested to be high in patients with severe ischemic heart disease. However, the sample size is insufficient, and further evaluation is necessary.

In the FOCUS study in patients undergoing hip surgery, of whom 63% had heart disease, setting a restrictive trigger was not useful.²⁷⁾ In an evaluation of patients with unstable coronary artery disease or myocardial infarction, the incidence of cardiovascular events and mortality rate tended to be lower in the non-restrictive trigger value group.³²⁾

While there are reports that the risk was not increased by setting a restrictive trigger in stable disease states, many of them were sub-group analyses in large-scale RCTs, or small-scale or single-center RCTs that varied in the outcome evaluation points and percentage of patients with cardiovascular complications. Until stronger evidence is established by repeating studies and evaluations by well-designed large-scale RCTs specific to the conditions of this CQ, a trigger higher than 8 g/dL is considered desirable.^{21,33)}

CQ1-9 What is the red blood cell transfusion trigger for anemia due to renal failure?

● Recommendation

For anemia due to renal failure, priority should be placed on treatment using ESAs and iron preparations; minimising transfusion, by avoiding it at $Hb \geq 7$ g/dL except in special cases, is recommended (2C). In candidates for future kidney transplantation, it is recommended to avoid red blood cell transfusion as much as possible (1C).

● Comment

Since there are no directly related reports, the evidence level is very low, but, if the condition is refractory to ESAs and iron preparations, which are usually expected to be effective in renal failure patients, it is necessary to determine the cause of the refractoriness, and if treatment is difficult, minimal necessary transfusion is performed with a Hb of 7 g/dL as a trigger, similar to other disorders.³⁴⁾ Transfusion should be avoided as much as possible in patients who may receive kidney transplantation.³⁵⁾ In massive transfusion or transfusion to children, measures to avoid hyperkalemia may be necessary.

CQ1-10 What is the red blood cell transfusion trigger for anemia due to surgery using an artificial heart-lung machine?

● Recommendation

Hb of 8-9 g/dL is recommended as a red blood cell transfusion trigger for anemia during the use of an artificial heart-lung machine (2C). However, maintaining the Hb \geq 9 g/dL must also be considered, depending on the preoperative cardiopulmonary function and patient's age (2C).

● Comment

In cardiovascular surgery, conclusions about the clinical superiority of restrictive transfusion (Hb \geq 7-8 g/dL) compared with liberal transfusion (Hb \leq 9-10 g/dL) are divided. According to the results of a recent RCT, the mortality rate was significantly reduced in the liberal transfusion group.³⁶⁾ On the other hand, according to the results of another relatively large-scale RCT, there was no difference in the survival rate or adverse events between the liberal and restrictive transfusion groups.³⁷⁾ This discrepancy among the reports may be derived from the heterogeneity of subject groups, and the superiority of restrictive transfusion is considered to vary with the contents of the risk including the

preoperative cardiac function (EuroSCORE, etc.). However, in elective coronary artery bypass surgery, no difference was reported in various outcomes between restrictive (trigger 7.5 g/dL) and liberal (9.0 g/dL) transfusions.³⁷⁾

CQ1-11 What is the red blood cell transfusion trigger for anemia in severely ill or septicemic patients?

● Recommendation

Hb of 7 g/dL is recommended as a red blood cell transfusion trigger for anemia in severely ill or septicemic patients (1B). In cancer patients, Hb of 9 g/dL should also be considered (2C).

● Comment

There are reports that compared the mortality rate and adverse events in severely ill patients such as those in the ICU and patients with septicemia who underwent red blood cell transfusion by restrictive (trigger Hb of 7-8 g/dL) and liberal (trigger Hb of 9-10 g/dL) approaches.^{23,30,38-41)} In cancer patients, the mortality rate was higher in the restrictive transfusion group⁴¹⁾ but was similar in other patients between the two groups. The incidences of infection and transfusion reactions were also lower in the restrictive transfusion group because of the low transfusion volume.

2) Does the storage duration of red blood cell products have any clinical effects?

● Recommendation

The storage duration of red blood cell products does not change the mortality rate or the incidence of complications or infections (1A). While the shelf life of red blood cell products in Japan is 21 days, clinical effects of its further prolongation are expected to be small (2C).

● Comment

Since the shelf life of red blood cell products is longer (35 or 42 days) in countries other than Japan, multi-center RCTs⁴²⁻⁴⁵⁾ concerning change in the mortality rate and incidences of complications, infections, etc., with the storage duration were carried out in Europe,⁴²⁾ Canada,^{42,44)} United States,^{43,44)} Australia,^{44,45)} and New Zealand.⁴⁵⁾ Average storage periods were 6.1, 7.8, 13.0, and 11.8 days, respectively, in the short-storage groups and 22.0, 28.3, 23.6, and 22.4 days in the long-storage groups, but no differences were observed in the mortality rate or incidence of complications, infection, etc. Meta-analyses and SRs⁴⁶⁻⁴⁸⁾ also showed no clinical effect of the difference in the storage duration, but one study reported that extravascular hemolysis did not increase during cold storage for a maximum of 35 days, but increased when the storage duration was 42 days.⁴⁹⁾ The shelf life of red blood cells has been defined as the period in which the intravascular survival of red blood cells 24 hours after administration is $\geq 70\%$.

3) Indications and recommendations of autologous blood donation in various disorders
CQ2-1 Is there an indication for autologous blood transfusion in orthopedic surgery (knee replacement, hip replacement, scoliosis surgery, etc.)?

● Recommendation

In artificial joint replacement, autologous blood transfusion by predeposit autologous donation has been recommended in Japan (2D) while autologous blood transfusion by perioperative cell salvage has been favored in Western countries (1B).

Recently, replacement transfusion volumes have been reduced by decreasing the volume of hemorrhage through the use of tranexamic acid, and patients who need no autologous blood transfusion may increase (1B).

● Comment

Autologous transfusion using blood processed after perioperative salvage has been reported to be effective for avoiding allogeneic blood transfusion by meta-analyses of RCTs.^{50,51)} However, according to RCTs carried out after 2015, operative blood loss has been reduced with the decrease in hemorrhage volume associated with the use of tranexamic acid in artificial knee^{52,53)} and hip replacement⁵⁴⁾, and patients who do not require autologous blood transfusion may increase. In Japan, however, autologous blood transfusion is promoted, and it should be considered in procedures such as scoliosis surgery (2C).

CQ2-2 Is there an indication for autologous blood transfusion in gynecological surgery (surgery for uterine myoma, uterine cancer, etc.)?

● Recommendation

Autologous blood transfusion by intraoperative cell salvage is recommended for surgical excision of uterine myoma with a large volume of hemorrhage (2C). In Japan, where preoperative autologous blood donation is widely practiced, papers with relevant evidence are few.

● Comment

The papers that evaluated autologous blood transfusion in the gynecological field are limited, but a single-center prospective observational study of 37 patients in Japan suggested the usefulness of autologous blood transfusion by intraoperative cell salvage in surgery for uterine myoma.⁵⁵⁾ In this study, autologous blood transfusion by intraoperative cell salvage was considered effective in 13 patients who lost 500 mL or more of blood, and the mean volume of hemorrhage in these patients was 842 mL.

CQ2-3 What are indications for autologous blood transfusion in obstetric surgery and the

volume of predeposited blood?

● Recommendation

Autologous blood transfusion (whether by preoperative donation, hemodilution, or perioperative cell salvage) is recommended for obstetric surgery associated with massive hemorrhage, such as surgery for placenta previa. Preoperative collection of 200-400 mL of blood per donation is recommended, with due consideration for the patient's body weight and other factors (1B). There are also favorable reports about cell salvage (2C).

● Comment

Autologous blood, even if predeposited, is often discarded, but wastage may be minimized by being selective about autologous collection. The implementation rate of autologous blood transfusion is high in patients with placenta previa.⁵⁶⁻⁵⁸⁾ Autologous transfusion has made it possible to avoid allogeneic blood even in surgery with a large volume of hemorrhage. Since the incidence of vagal reflex is high in pregnant women during autologous blood donation, the volume of blood collected at a time should be determined with due consideration of body weight and other factors. Autologous blood transfusion by cell salvage is useful particularly in hysterectomy following Caesarean section.⁵⁹⁾

CQ2-4 Can autologous blood transfusion be recommended in cardiovascular surgery (open-heart surgery, etc.)?

● Recommendation

In cardiovascular surgery (open-heart surgery, etc.), autologous blood transfusion by intra/postoperative cell salvage is recommended as a means to reduce or avoid allogeneic blood transfusion (1B).

● Comment

In cardiovascular surgery (open-heart surgery, etc.), autologous blood transfusion by perioperative cell salvage (including the combined use of cell salvage and hemodilution) has been shown to reduce the volume of allogeneic blood transfusion.⁶⁰⁻⁶³⁾ While no increase in the volume of hemorrhage or the frequency of clotting disorders or infection has been noted in cell saver autologous blood transfusions in general cardiovascular surgery, there has also been a report that clotting disorders and the volume of hemorrhage increased in procedures with a high risk of bleeding.⁶³⁾ It is necessary to understand indications and contraindications and carefully perform transfusion by referring to the Practice Guidelines for Cell Salvage Autologous Blood Transfusion (2012) of the Japanese Society of Autologous Blood Transfusion.

CQ2-5 Can autologous blood transfusion be recommended in surgeries that involve bleeding such as colectomy and hepatectomy?

● Recommendation

Autologous blood transfusion contributes to a reduction or avoidance of allogeneic blood transfusion in surgeries that involve considerable bleeding such as colectomy and hepatectomy (2D).

● Comment

No difference is observed in the frequency of adverse events between autologous and allogeneic blood transfusions in surgeries of colon cancer,⁶⁴⁾ esophageal cancer,⁶⁵⁾ liver cancer,⁶⁴⁾⁶⁶⁾ head and neck cancer,⁶⁴⁾⁶⁷⁾ etc. However, according to the Practice Guidelines for Cell Salvage Autologous Blood Transfusion (2012) of the Japanese Society of Autologous Blood Transfusion, autologous blood transfusion is "contraindicated when there is contamination by bacteria or malignant tumor cells," and caution is considered necessary in its implementation. However, as for the question of

whether events such as metastasis are increased by cell salvage autologous blood transfusion in surgery of cancer patients, a meta-analysis denied such a tendency.⁶⁴⁾

Points of Revision in the 2nd Edition Compared with the 1st Edition

1. Reduction of 2 authors
2. Change of affiliation of 2 authors
- 3.

1. Introduction

1) Objectives of the preparation of the guidelines

The sections of PBM and autologous blood transfusion were revised and supplemented.

2) Circumstances of the guidelines preparation

Supplementation of the latter part

3) Preparation committee members

COI were changed and corrected.

4) Preparation methods

● Setting of clinical questions (CQs)

A CQ concerning anemia of pregnant women was eliminated. An item concerning whether the storage period of red blood cell products has any effects was added.

● Search of databases This item was added.

● Establishment of literature search formula This item was added.

● Screening and literature management This item was added.

● Evidence as a whole and its summary This item was added.

5) Publication and revision

No change

6) Funding and conflicts of interest

No change

4.

2. Types of red blood cell products and evaluation of their administration

Partial revision of calculation formulas

5.

3. Guidelines for red blood cell products

1) Trigger values for the use of red blood cell products and recommendations for various disorders

CQ1-1 Recommendation: Partially supplemented Comment: No change

CQ1-2 Recommendation: Partially supplemented Comment: Partially supplemented

CQ1-3 Recommendation: Partially revised Comment: Partially supplemented

CQ1-4 No change

CQ1-5 Recommendation: Partially revised Comment: Partially revised

CQ1-6, CQ1-7, CQ1-8 No change

CQ1-9 Recommendation: Partially supplemented Comment: Partially supplemented

CQ1-10 Entirely revised

CQ1-11 Recommendation: Partially supplemented Comment: Partially supplemented

2) Does the duration of storage period of red blood cell products have any clinical effects?

Newly added

3) Indications and recommendations of autologous blood donation in various disorders

CQ2-1 Recommendation: Partially revised Comment: Partially revised

CQ2-2 No change

CQ2-3 Recommendation: Partially supplemented Comment: Partially supplemented

CQ2-4 Recommendation: Partially revised Comment: Partially revised

CQ2-5 Recommendation: Partially revised Comment: Partially revised

References

- 1) Yuji Yonemura, Masanori Matsumoto, Eiichi Inada, et al.: Guidelines for the use of red blood cell products based on scientific evidence. JJTC. 2016;62;641-650.
- 2) Tsuguya Fukui and Naohito Yamaguchi: Minds Handbook for Clinical Practice Guideline Development 2014 Igaku-Shoin Ltd. 2014.
- 3) “Clinical Practice Guidelines for Refractory Anemia” Editorial Committee: Clinical Practice Guidelines for Refractory Anemia - Latest Trends of Disease State, Diagnosis, and Treatment of Idiopathic Hematopoietic Disorders. Nankodo Co., Ltd. 2011.
- 4) Simon TL, Alverson DC, AuBuchon J, et al: Practice parameter for the use of red blood cell transfusions: Developed by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists Arch Pathol Lab Med, 1998;122:130-138.
- 5) Murphy MF, Wallington TB, Kelsey P, et al: Guidelines for the clinical use of red cell transfusions. Brit J Haematol, 2001;113:24-31.
- 6) Research representative: Keiyo Ozawa, Research Project to Conquer Intractable Diseases subsidized by Health and Welfare Sciences Research Grants, Research on Idiopathic Hematopoietic Disorders (2008) Clinical Practice Guidelines for Post-transfusion Iron Overload, 2008.
- 7) Jang JH, Harada H, Shibayama H, et al: A randomized controlled trial comparing darbepoetin alfa doses in red blood cell transfusion-dependent

patients with low- or intermediate-1 risk myelodysplastic syndromes.

Int J Hematol, 2015;102:401-412.

- 8) Luan H, Ye F, Wu L, et al: Perioperative blood transfusion adversely affects prognosis after resection of lung cancer: a systematic review and a meta-analysis.
Database of Abstracts of Reviews of Effects, 2014;34.
- 9) Acheson AG, Brookes MJ, Spahn DR: Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Annals of Surg, 2012;256:235-244.
- 10) Kneuert PJ, Patel SH, Chu CK, et al: Effects of perioperative red blood cell transfusion on disease recurrence and survival after pancreaticoduodenectomy for ductal adenocarcinoma. Annals Surgical Oncol, 2011;18:1327-1334.
- 11) Dresner SM, Lamb PJ, Shenfine J, et al: Prognostic significance of perioperative blood transfusion following radical resection for oesophageal carcinoma.
Eur Surg Oncol, 2000;26:492-497.
- 12) Chau JK, Harris JR, Seikaly HR: Transfusion as a predictor of recurrence and survival in head and neck cancer surgery patients.
J Otolaryngology, 2010;39:516-522.
- 13) Warner LL, Dowdy SC, Martin JR, et al: The impact of perioperative packed red blood cell transfusion on survival in epithelial ovarian cancer.
Int J Gynecol Cancer, 2013;23:1612-1619.

- 14) Rodgers III GM, Becker PS, Blinder M, et al: Cancer- and Chemotherapy- Induced Anemia. Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network, 2012;10:628-653.
- 15) Hoeks MPA, Kranenburg FJ, Middelburg RA: Impact of red blood cell transfusion strategies in haemato-oncological patients: a systematic review and meta-analysis. Brit J Haematol, 2017;78:137-151.
- 16) Estcourt LJ, Malouf R, Trivella M, et al: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support. Cochrane Database of Systematic Reviews CD011305, 2017
- 17) Robitaille N, Lacroix J, Alexandrov L, et al: Excess of veno-occlusive disease in a randomized clinical trial on a higher trigger for red blood cell transfusion after bone marrow transplantation: A Canadian blood and marrow transplant group trial. Biol Blood Marrow Transplant, 2013;19:468-473.
- 18) Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories in Japan (2nd edition) <http://yuketsu.jstmct.or.jp/wp-content/uploads/2016/10/5bc721e299263f6d44e2215cbdffbfaf.pdf>
- 19) Ness PM: How do I encourage clinicians to transfuse mismatched blood to patients with autoimmune hemolytic anemia in urgent situations? Transfusion, 2006;46:1859-1862.
- 20) Park SH, Choe WH, Kwon SW: Red blood cell transfusion in patients with

autoantibodies: Is it effective and safe without increasing hemolytic risk?

Ann Lab Med, 2015;35:436-444.

- 21) Carson JL, Stanworth SJ, Roubinian N, et al: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion, The Cochrane database of systematic reviews, 2016;10:1-115.
- 22) Villanueva C, Colomo A, Bosch A, et al: Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med, 2013;368:11-21.
- 23) Carson JL, Guyatt G, Heddle NM, et al: Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA, 2016;316:2025-2035.
- 24) Jairath V, Kahan BC, Gray A, Doré CJ, et al: Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet, 2015;386:137-144.
- 25) Holst LB, Petersen MW, Haase N, et al: Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ, 2015;350:h1354.
- 26) Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med, 1999;340:409-417.
- 27) Carson JL, Terrin ML, Noveck H, et al: Liberal or Restrictive transfusion in high-

- risk patients after hip surgery.
N Engl J Med, 2011;365:2453-2462.
- 28) Brunskill SJ, Millette SL, Shokoohi A, et al: Red blood cell transfusion for people undergoing hip fracture surgery.
The Cochrane database of systematic reviews, 2015;4:1-54.
- 29) Carson JL, Sieber F, Cook DR, et al: Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from FOCUS randomized controlled trial.
Lancet, 2015;385:1183-1189.
- 30) Hovaguimian F, Myles PS: Restrictive versus liberal transfusion strategy in the perioperative and acute care settings; a context-specific systematic review and meta-analysis of randomized controlled trials. Anesthesiology, 2016;125:46-61.
- 31) Hebert PC, Yetisir E, Martin C, et al: Is a low transfusion threshold safe in critically ill patients with cardiovascular disease?
Crit Care Med, 2001;29:227-234.
- 32) Carson JL, Brooks MM, Abbott JD, et al: Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease.
Am Heart J, 2013;165:964-971.
- 33) Docherty AB, O'Donnell R, Brunskill S, et al.: Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting; systematic review and meta-analysis.
BMJ, 2016;352;i1351:1-11.
- 34) Guideline for Renal Anemia in Chronic Kidney Disease. J. Jpn. Soc. Dial. Ther., 2016;49:89-158.

- 35) Balasubramaniam GS, Morris M, Gupta A, et al. Allo-sensitization rate of male patients awaiting first kidney grafts after leuko-depleted blood transfusion. *Transplantation*, 2012;93:418–422.
- 36) Reeves BC, Pike K, Rogers CA, et al: Stokes EA, Wordsworth S, Nash RL, Miles A, Mumford AD, Cohen A, Angelini GD, Murphy GJ. A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2). *Health Technol Asses.*, 2016;20(60):1-260.
- 37) Mazer CD, Whitlock RP, Fergusson DA, et al: TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. *N Engl J Med*, 2017;377:2133-2144.
- 38) Holst LB, Haase N, Wetterslev J, et al: Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*, 2014;371:1381-1391.
- 39) Mouncey PR, Osborn TM, Power GS, et al: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*, 2015;372:1301-1311.
- 40) Hsu CY, Liu SH, Chao CH, et al: STROBE-compliant article: Blood transfusions within the first 24 hours of hospitalization did not impact mortality among patients with severe sepsis. *Medicine (United States)* 2016;95:1-7.
- 41) Bergamin FS, Almeida JP, Landoni G, et al: Liberal Versus Restrictive

- Transfusion Strategy in Critically Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial. *Critical care medicine* 2017;45:766-773.
- 42) Lacroix J, Herbert PC, Fergusson DA, et al: Age of transfused blood in critically ill adults. *N Engl J Med*, 2015;372:1410-1418.
- 43) Steiner ME, Ness PM, Assmann SF, et al: Effect of Red-Cell Storage Duration on Patients Undergoing Cardiac Surgery. *N Engl J Med*, 2015;372:1419-1429.
- 44) Heddle NM, Cook RJ, Arnold DM, et al: Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion. *N Engl J Med*. 2016;375:1937-1945.
- 45) Cooper DJ, McQuilten ZK, Nichol A, et al: Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults. *N Engl J Med*, 2017;377:1858-1867.
- 46) Alexander PE, Barty R, Fei Y, et al: Transfusion of fresher vs older red blood cells in hospitalized patients: a systematic review and meta-analysis. *Blood*, 2016;127:400-410.
- 47) Carson JL, Guyatt G, Heddle NM, et al: Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*, 2016;316:2025-2035.
- 48) Chai-Adisaksopha C, Alexander PE, Guyatt G, et al: Mortality outcomes in patients transfused with fresher versus older red blood cells: a meta-analysis. *Vox sanguinis*, 2017;112:268-278.

- 49) Rapido F, Brittenham GM, Bandyopadhyay S, et al: Prolonged red cell storage before transfusion increases extravascular hemolysis.
JCI, 2017;127:375-382.
- 50) Markar SR, Jones GG, Karthikesalingam A, et al: Transfusion drains versus suction drains in total knee replacement: meta-analysis.
Knee Surg Sports Traumatol Arthrosc, 2012;20:1766-1772.
- 51) Haien Z, Yong J, Baoan M, et al: Post-operative auto- transfusion in total hip or knee arthroplasty: a meta-analysis of randomized controlled trials.
PLoS ONE, 2013;8:1-9.
- 52) Yang Y, Lv Y-M, Ding P-J, et al: The reduction in blood loss with intra-articular injection of tranexamic acid in unilateral total knee arthroplasty without operative drains: a randomized controlled trial.
Eur J Orthop Surg Traumatol, 2015;25:135-139.
- 53) Gao F, Sun W, Guo W, et al: Topical administration of tranexamic acid plus diluted-epinephrine in primary total knee arthroplasty: a randomized double-blinded controlled trial.
J Arthroplasty, 2015;30:1354-1358.
- 54) Yi Z, Bin S, Jing Y, et al: Tranexamic acid administration in primary total hip arthroplasty.
J Bone Joint Surg Am, 2016;98:983-991.
- 55) Yamada T, Yamashita Y, Terai Y, et al: Intraoperative blood salvage in abdominal uterine myomectomy.
Int J Gynecol & Obstet, 1997;56:141-145.
- 56) Watanabe N, Suzuki T, Ogawa K, et al: Five-year study assessing the feasibility

and safety of autologous blood transfusion in pregnant Japanese women.

J Obstet Gynaecol Res, 2011;37:1773-1777.

- 57) Yamamoto Y, Yamashita T, Tsuno NH, et al: Safety and efficacy of preoperative autologous blood donation for high-risk pregnant women: Experience of a large university hospital in Japan.

J Obstet Gynaecol Res, 2014;40:1308-1316.

- 58) Ryuji Kawaguchi, Haruki Nakamura, Kana Iwai, et al.: **Present State of Predeposit Autologous Blood Transfusion in the Gynecological Field and its Problems.**

Jpn J Obstet Gynaecol Neonatal Hematol, 2014;24:14-15.

- 59) Milne ME, Yazer MH, Waters JH: Red blood cell salvage during obstetric hemorrhage.

Obstetrics and gynecology, 2015;125:919-923.

- 60) Dalrymple-Hay MJ, Pack L, Deakin CD et al: Autotransfusion of washed shed mediastinal fluid decreases the requirement for autologous blood transfusion following cardiac surgery: a prospective randomized trial.

Eur J Cardiothorac Surg, 1999;15:830-834.

- 61) Wong JC, Torella F, Haynes SL et al: Autologous versus allogeneic transfusion in aortic surgery: a multicenter randomized clinical trial.

Ann Surg, 2002;235:145-51.

- 62) Niranjana G, Asimakopoulos G, Karagounis A et al: Effects of cell saver autologous blood transfusion on blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial.

- Eur J Cardiothorac Surg, 2006;30:271-277.
- 63) Shen S, Zhang J, Wang W et al: Impact of intra-operative cell salvage on blood coagulation in high-bleeding-risk patients undergoing cardiac surgery with cardiopulmonary bypass: A prospective randomized and controlled trial.
J Transl Med, 2016;14:228.
- 64) Waters JH, Yazer M, Chen YF, et al: Blood salvage and cancer surgery: a meta-analysis of available studies. Transfusion, 2012;52:2167-2173.
- 65) Kinoshita Y, Udagawa H, Tsutsumi K, et al: Usefulness of autologous blood transfusion for avoiding allogenic transfusion and infectious complications after esophageal cancer resection.
Surgery, 2000;127:185-192.
- 66) Park JO, Gonen M, D'Angelica MI, et al: Autologous versus allogeneic transfusions: no difference in perioperative outcome after partial hepatectomy.
Autologous transfusion on hepatectomy outcome.
J Gastrointestinal Surg, 2007;11:1286-1293.
- 67) Keiko Ohya, Hideo Shigemi, Takeshi Suko, et al.: Autologous blood transfusion for head and neck cancer patients.
Otologia Fukuoka, 1999;45:113-116.