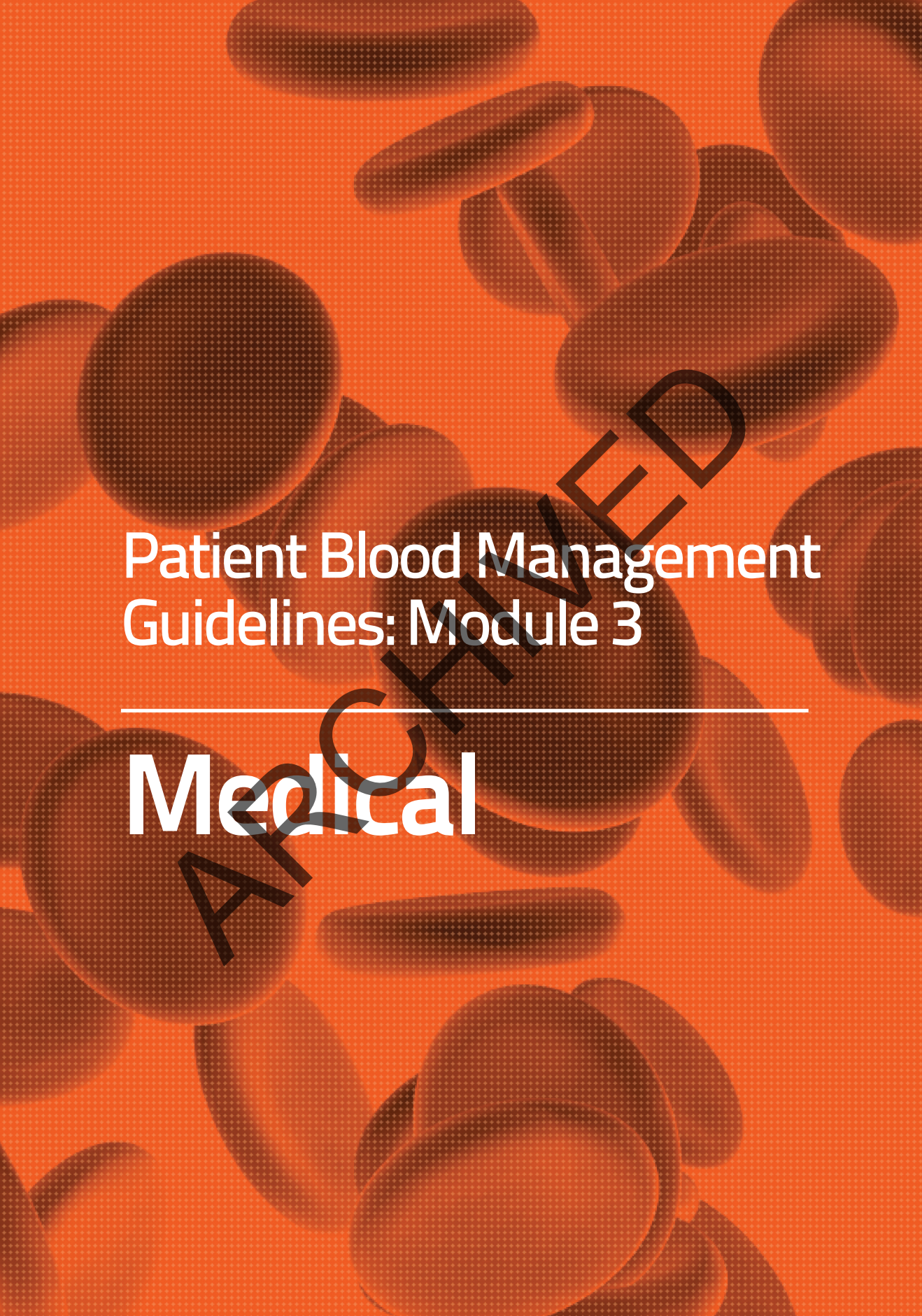




Patient Blood Management Guidelines: Module 3

Medical

© National Blood Authority, 2012.



With the exception of any logos and registered trademarks, and where otherwise noted, all material presented in this document is provided under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Australia (<http://creativecommons.org/licenses/by-nc-sa/3.0/au/>) licence.

You are free to copy, communicate and adapt the work for noncommercial purposes, as long as you attribute the authors and distribute any derivative work (i.e. new work based on this work) only under this licence.

If you adapt this work in any way or include it in a collection, and publish, distribute or otherwise disseminate that adaptation or collection to the public, it should be attributed in the following way:



This work is based on/includes the *National Blood Authority's Patient Blood Management Guideline: Module 3 Medical*, which is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Australia licence.

Where this work is not modified or changed, it should be attributed in the following way:



© National Blood Authority, 2012.

Reprinted with corrections 2013.

ISBN 978-0-9872519-8-5

For more information:

Patient Blood Management Guidelines

National Blood Authority

Locked Bag 8430

Canberra ACT 2601

Telephone: +61 2 6151 5000

Email: guidelines@blood.gov.au

Website: www.blood.gov.au

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. Recommendations contained herein are based on the best available evidence published between 1966 and July 2010. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

Publication approval



Australian Government

National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 18 July 2012, under Section 14A of the *National Health and Medical Research Council Act 1992*. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Patient Blood Management Guidelines:

Module 3 – Medical

This module was developed through clinical input and expertise of representatives from the colleges and societies listed below, a patient blood management advocate, an independent gastroenterology expert and an independent nephrology expert (see Appendix A).

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Blood Transfusion

Australian Red Cross Blood Service

College of Intensive Care Medicine of Australia and New Zealand

Haematology Society of Australia and New Zealand

Royal Australian College of General Practitioners

Royal Australasian College of Physicians

Royal College of Nursing Australia

Royal College of Pathologists of Australasia

Thalassaemia Australia

The National Blood Authority gratefully acknowledges these contributions. College and society endorsement of this module can be found at www.blood.gov.au.



Funding, secretariat and project management was provided by the National Blood Authority, Australia. The development of the final recommendations has not been influenced by the views or interests of the funding body.

ARCHIVED

Abbreviations and acronyms

ACS	acute coronary syndrome
AHCDO	Australian Haemophilia Centre Directors' Organisation
AHMAC	Australian Health Ministers' Advisory Council
AIDS	acquired immunodeficiency syndrome
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ASBT	Australasian Society of Blood Transfusion
CARI	Caring for Australians with Renal Impairment
CHF	chronic heart failure
CKD	chronic kidney disease
COI	conflict of interest
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
ES	evidence statement
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FACT	Functional Assessment of Cancer Therapy
FFP	fresh frozen plasma
FID	functional iron deficiency
Hb	haemoglobin
HIF	hypoxia-inducible factor
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HSCT	haematopoietic stem cell transplantation
IBD	inflammatory bowel disease
IV	intravenous
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MDS	myelodysplastic syndrome
MI	myocardial infarction
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council

NYHA	New York Heart Association
NZBS	New Zealand Blood Service
PBS	Pharmaceutical Benefits Scheme
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
SCoH	Standing Committee on Health
SF-36	Short Form-36
TGA	Therapeutic Goods Administration
TTP	thrombotic thrombocytopenic purpura
WHO	World Health Organization

ARCHIVED

Contents

Abbreviations and acronyms

Executive summary	1
--------------------------	----------

Summary of recommendations and practice points	2
---	----------

1	Introduction	15
1.1	Development of the guidelines	16
1.2	Governance structure	17
1.3	Structure of the document and related materials	17
1.3.1	The document	17
1.3.2	Related materials	18
2	Methods	21
2.1	Clinical research questions – development and details	22
2.2	Review and research	22
2.2.1	Systematic review process	22
2.2.2	Background material	23
2.3	Development of evidence statements, recommendations and practice points	24
3	Clinical guidance	27
3.1	Effect of anaemia on outcomes	28
3.1.1	Acute coronary syndrome	28
3.1.2	Heart failure	29
3.1.3	Community-dwelling elderly	30
3.1.4	Cancer	30
3.1.5	Renal	31
3.2	Effect of red blood cell transfusion on outcomes	32
3.2.1	Medical population	32
3.2.2	Acute coronary syndrome	34
3.2.3	Heart failure	35
3.2.4	Cancer	36
3.2.5	Acute upper gastrointestinal blood loss	37
3.3	Effect of erythropoiesis - stimulating agents and iron	38
3.3.1	Cancer	39
3.3.2	Chronic heart failure	41
3.3.3	Chronic kidney disease	44
3.3.4	Elderly patients	47
3.3.5	Inflammatory bowel disease	48
3.3.6	Myelodysplastic syndrome	49
3.3.7	Other populations	49
3.4	Effect of blood components on outcomes	50
3.4.1	Fresh frozen plasma	50
3.4.2	Fibrinogen and cryoprecipitate	52
3.4.3	Platelet transfusion	53

3.5	Blood component transfusion	55
3.5.1	Coagulation parameters and fresh frozen plasma transfusion	56
3.5.2	Fibrinogen level and use of cryoprecipitate or fibrinogen concentrate	57
3.5.3	Platelet count and prophylactic platelet transfusion in patients undergoing chemotherapy and haematopoietic stem cell transplantation	58
3.6	Red blood cell transfusion in chronically transfused patients	60
3.6.1	Thalassaemia	60
3.6.2	Myelodysplasia	62
4	Background questions	65
4.1	Interventions to raise haemoglobin levels in patients with malignancies	66
4.1.1	Tumour hypoxia: pathophysiology and effects	66
4.1.2	Tumour hypoxia and radiotherapy resistance	66
4.1.3	Impact of correction of anaemia on radiotherapy outcome	67
4.2	Assessment of patients after red blood cell transfusion	68
5	Future directions	71
5.1	Evidence gaps and areas of future research	72
5.2	Topics for future consideration	72
6	Implementing, evaluating and maintaining the guidelines	75
Appendix A	Governance	79
Appendix B	Transfusion risks in the context of patient blood management	87
Appendix C	Blood sectors	91
Appendix D	Process report	97
Appendix E	Product information	101
Appendix F	Summary of recommendations and practice points by clinical condition	103
References		119
Tables		
Table 1.1	Phases of development of guideline modules	16
Table 2.1	Body of evidence matrix	25
Table 2.2	Definitions of NHMRC grades for recommendations	25
Table B.1	Transfusion risks	88
Table B.2	Calman Chart ^a (United Kingdom risk per one year)	89
Figures		
Figure A1	Management framework for development of the guidelines	80

Executive summary

This document, *Patient Blood Management Guidelines: Module 3 – Medical*, is the third in a series of six modules that focus on evidence-based patient blood management. The other five modules are critical bleeding/massive transfusion, perioperative, critical care, obstetrics and paediatrics (including neonates). Together, Module 2 (Perioperative) and Module 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*¹ (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

This document was developed by a Clinical/Consumer Reference Group (CRG) representing specialist colleges, organisations and societies, with the active participation of the clinical community.

This executive summary includes:

- a summary of the *recommendations* that were developed by the CRG, based on evidence from a systematic review
- a summary of the *practice points* that were developed by the CRG through consensus decision making.

Details of the systematic reviews used in the development of this module are given in the two-volume technical report that accompanies this document.

Materials relevant to consumers and to clinicians managing medical patients will be developed to accompany this module; these materials will be available online and in print.

ARCHIVED

Summary of recommendations and practice points

The CRG developed recommendations where sufficient evidence was available from the systematic review of the literature. The recommendations have been carefully worded to reflect the strength of the body of evidence. Each recommendation has been given a grade, using the following definitions, set by the NHMRC:

GRADE A	Body of evidence can be trusted to guide practice
GRADE B	Body of evidence can be trusted to guide practice in most situations
GRADE C	Body of evidence provides some support for recommendation(s), but care should be taken in its application
GRADE D	Body of evidence is weak and recommendations must be applied with caution.

The CRG developed practice points where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but the CRG felt that clinicians require guidance to ensure good clinical practice. These points are based on consensus among the members of the committee.

Appendix F gives the recommendations and practice points by clinical condition.

Recommendations

IDENTIFIER AND GRADE	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalasassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
R1 GRADE C	In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.	3.2.2	✓									
R2 GRADE A	In cancer patients with anaemia, the routine use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.	3.3.1		✓								
R3 GRADE B	In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. This is consistent with the 2011 update to the <i>Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia</i> , 2006. ² Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.	3.3.2		✓								
R4 GRADE B	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient. Note: The CARI guidelines recommend a Hb target between 100–115 g/L ⁵	3.3.3						✓				

Recommendations

CONDITIONS

IDENTIFIER AND GRADE	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassemia and myelodysplasia	Coagulopathy	Thrombocytopenia
R5 GRADE C	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to relieve fatigue, after consideration of risks and benefits for the individual patient. Note: The CARI guidelines recommend a Hb target between 100–115 g/L.	3.3.3						✓				
R6 GRADE B	In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.	3.3.3						✓				
R7 GRADE B	In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the routine use of ESAs is not recommended because of the increased risk of cancer-related mortality.	3.3.3						✓				
R8 GRADE B	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9/L$ in the absence of risk factors, and at $<20 \times 10^9/L$ in the presence of risk factors (e.g. fever, minor bleeding).	3.5.3							✓			

ACS, acute coronary syndrome; CHF, chronic heart failure; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association; R, recommendation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

Practice points

ARCHIVED

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia

Practice points

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1	✓		✓	✓	✓	✓	✓			

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1	✓	✓	✓	✓	✓	✓	✓			
PP5	In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. (See PP1 and PP2).	3.2.2		✓								
PP6	In patients with ACS and a Hb concentration of 80 – 100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits. (See PP1 and PP2).	3.2.2		✓								
PP7	In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status. For further guidance on how to manage patients with heart failure, refer to general medical or ACS sections, as appropriate (R1, R3, PP3–PP6).	3.2.3										
PP8	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.	3.2.4 3.3.1				✓						

Practice points

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalasassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP9	There is a lack of specific evidence relating to the effects of RBC transfusion in patients with cancer. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia. When treating patients with cancer, refer also to the general medical population PP1–PP4.	3.2.4				✓						
PP10	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. Therefore, a more restrictive approach may be appropriate. There are no data to support a specific Hb treatment target in these patients.	3.2.5				✓						
PP11	For critically bleeding patients, refer to <i>Patient Blood Management Guidelines; Module 1 – Critical Bleeding/Massive Transfusion</i> (2011). ⁴	3.2.5				✓						
PP12	In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.	3.3.1				✓						
PP13	ESA use is less effective in patients with chronic renal failure who have absolute or functional iron deficiency.	3.3.3						✓				
PP14	For comprehensive information about ESA and iron therapy in patients with CKD, refer to CARI iron guidelines. ⁵	3.3.3						✓				

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalasassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP15	In patients with IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.	3.3.5					✓					
PP16	The routine use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment. The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.	3.4.1									✓	

Practice points

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalasassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP17	For guidance on the use of FFP in specific patient groups, refer to: ▪ Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)⁴ ▪ Patient Blood Management Guidelines: Module 2 – Perioperative (2012)⁶ ▪ Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)⁷ ▪ AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) ▪ TTP: Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004).⁸	3.4.1									✓	
PP18	The routine use of cryoprecipitate or fibrinogen concentrate in medical patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified; where transfusion is considered necessary, the risks and benefits should be considered for each patient. Specialist opinion is advised for the management of DIC.	3.4.2									✓	

ARCHIVED

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS
PP19	For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to: ▪ <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion</i> (2011)⁴ ▪ AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) ▪ <i>TTP: Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004)⁸	3.4.2	General medical Cardiac – acute coronary syndrome Heart failure Cancer Gastrointestinal Chronic kidney disease Chemotherapy and haematopoietic stem cell transplantation Thalasassaemia and myelodysplasia Coagulopathy Thrombocytopenia
PP20	Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.	3.4.3	

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP21	In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.⁹ Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness). Therapeutic platelet transfusions could be considered for treatment of bleeding.	3.4.3								✓		✓
PP22	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, there is no evidence to support: - a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding) - a strategy of therapeutic-only platelet transfusions (i.e. for treatment of clinically significant bleeding). Further research to determine the safety and efficacy of a lower platelet transfusion trigger is underway.	3.5.3							✓			

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
PP23	In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.	3.6.1								✓		
PP24	In patients with myelodysplasia who are regularly and chronically transfused, there is no evidence to guide particular Hb thresholds. Decisions around appropriate triggers and frequency of transfusion need to be individualised, taking into account anaemia-related symptoms, functional or performance status, and the patient's response to previous transfusions.	3.6.2								✓		

ACS, acute coronary syndrome; AHCD0, Australian Haemophilia Centre Directors' Organisation; CARI, Caring for Australasians with Renal Impairment; CHF, chronic heart failure; CKD, chronic kidney disease; CRG, Clinical/Consumer Reference Group; DIC, disseminated intravascular coagulation; ESA, erythropoiesis-stimulating agent; FFP, fresh frozen plasma; Hb, haemoglobin; HIT, heparin-induced thrombocytopenia; IBD, inflammatory bowel disease; IV, intravenous; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

ARCHIVED

1 Introduction

Patient blood management aims to improve clinical outcomes by avoiding unnecessary exposure to blood components. It includes the three pillars of:

- optimisation of blood volume and red cell mass
- minimisation of blood loss
- optimisation of the patient's tolerance of anaemia.

Patient blood management optimises the use of donor blood and reduces transfusion-associated risk.

If the patient requires therapy for anaemia, thrombocytopaenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks (Appendix B). In the process of obtaining informed consent, a clinician should allow the patient sufficient time to ask questions, and should answer those questions.

This document, *Patient Blood Management Guidelines: Module 3 – Medical*, is the third in a series of six modules that focus on evidence-based patient blood management. The other five modules are listed in Table 1.1, below. Together, Module 2 (Perioperative) and Module 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*¹ (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

This module is intended to assist and guide clinical decisions and coordination of health-care across the primary, secondary and tertiary care settings for patients with acute or chronic medical conditions requiring haematological intervention. Transfusion decisions for patients should also take into account each individual's clinical circumstances and physiological status, and their treatment preferences and choices.

Revision of the 2001 guidelines¹ was needed because of the:

- increasing evidence of transfusion-related adverse outcomes, leading to the emergence of new practices, including restrictive transfusion strategies and the increased use of alternatives to transfusion in the management of anaemia
- variable (and frequently poor) compliance with the recommendations of the guidelines, indicated by a high degree of variation in transfusion practices
- failure of the guidelines to address a range of clinical settings where blood management is commonly required, including critical bleeding and massive transfusion, chronic medical conditions, obstetrics and paediatrics.

1.1 Development of the guidelines

In response to the situation outlined above, the NHMRC, the Australia & New Zealand Society of Blood Transfusion (ANZSBT) and the National Blood Authority (NBA)^a agreed to develop a series of six patient-focused, evidence-based modules that together comprise new patient blood management guidelines.

The six modules of the guidelines are being developed in three phases, as shown in Table 1.1.

Table 1.1 Phases of development of guideline modules

PHASE	MODULES
I	1 – Critical Bleeding/Massive Transfusion 2 – Perioperative
II	3 – Medical 4 – Critical Care
III	5 – Obstetrics 6 – Paediatrics/Neonates

^a The structure of the Australian blood sector is outlined in Appendix C.

1.2 Governance structure

A multilevel management framework was established by the NBA to coordinate the development of the new patient blood management guidelines. The management framework (illustrated in Appendix A) consists of:

- a Steering Committee, responsible for the overall development and governance of the entire project
- an Expert Working Group (EWG), responsible for clinical oversight and integration of the six modules
- Clinical/Consumer Reference Groups (CRGs – one for each of the six modules), with membership including representation from relevant colleges, societies and consumer groups, to provide expert knowledge and input
- systematic reviewers and a technical writer, contracted by the NBA to review the literature and develop a draft of each module
- an independent systematic review expert, to provide advice and mentoring to the systematic reviewers, technical writer, EWG and CRGs; and to ensure that the development process and the revised guidelines comply with NHMRC requirements.

The NBA provided the secretariat, project funding and project management. The NBA website includes a list of colleges and societies that have endorsed these guidelines.^b Appendix A lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 6.

1.3 Structure of the document and related materials

1.3.1 The document

This module includes:

- *recommendations* – based on evidence from the systematic review
- *practice points* – based on consensus decision making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but where it was considered that clinicians require guidance to ensure good clinical practice.

The recommendations and practice points are summarised in the Executive summary, and given by clinical condition in Appendix F.

The remainder of this document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG, and recommendations and practice points, as appropriate (Chapter 3)

^b <http://www.blood.gov.au/>

- background material on clinical issues not covered by the systematic review (Chapter 4)
- recommendations for future directions (Chapter 5)
- information on implementing, evaluating and maintaining the guidelines (Chapter 6).

The document also includes appendixes that provide an overview of the blood sectors in Australia and New Zealand, membership of the governance bodies for guideline development, information on transfusion risks, a process report, information about blood components and the recommendations and practice points listed by clinical condition. Finally, the document contains a list of references.

1.3.2 Related materials

Materials relevant to clinicians will be developed to accompany this module; these materials will be available online and in print from the NBA.

The technical report that underpins this document is available online, in two volumes:

- *Volume 1*
This volume contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline.¹⁰
- *Volume 2*
This volume contains appendixes that document the literature searches, study quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.¹¹

ARCHIVED

ARCHIVED

ARCHIVED

2 Methods

The development of evidence-based clinical practice guidelines that meet NHMRC standards involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence.¹² The methods used in applying this process to the development of this module are outlined below, and are given in full in the accompanying technical reports. A summary of the overall process for development of this module is given in Appendix D.

2.1 Clinical research questions – development and details

Between April and June 2009, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the EWG, the independent systematic review expert and the CRG (Appendix A). The process resulted in two different types of questions – those that are specific to this module, and those that are generic (i.e. relevant to all six modules that make up the guidelines).

The specific and generic questions were crafted in such a way that they attempted to provide answers in clinically relevant areas of uncertainty. The questions were further refined through consultation among the systematic reviewer, CRG, NBA and independent systematic review expert. Details of research question criteria are presented in Volume 1 of the technical report.¹⁰

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken to attempt to answer the question specific to medical transfusion, and the generic questions relevant to all six modules. The systematic review questions are listed in Box 2.1.

To answer these questions, comprehensive search strategies were designed, as detailed in Volume 2 of the technical report. Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant, and literature recommended by expert members of the CRG. The search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically.

The systematic review included only data from studies that met the relevant inclusion criteria, were of adequate quality, and were published between 1966 and July 2010. Identification of relevant evidence and assessment of evidence was conducted in accordance with NHMRC standards and procedures for externally developed guidelines.¹³

The question 'What is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate?' was not included in this review, but was covered (as Question 6) in the document *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion*.⁴

Box 2.1 Systematic review questions

Questions 1 – 5 are relevant to all six modules of these guidelines; Question 6 is specific to medical transfusion (i.e. to this module).

- **Question 1** – In medical patients, is anaemia an independent risk factor for adverse outcomes? (Aetiological question)
- **Question 2** – In medical patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- **Question 3** – In medical patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- **Question 4** – In medical patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- **Question 5** – In medical patients, at what INR (PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events? (Interventional and Prognostic question)
- **Question 6** – In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes? (Interventional question)

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; Hb, haemoglobin; INR, international normalised ratio; PT, prothrombin time; RBC, red blood cell

2.2.2 Background material

Material relevant to background questions was gathered by fellows or registrars under the supervision of CRG members. Sources included medical textbooks, grey literature, published scientific and review articles, series yearbooks and other relevant medical literature; however, systematic review processes were not applied. The questions researched are listed in Box 2.2.

Box 2.2 Background research questions

- **Background question 1** – In patients with malignancies (solid tumours) undergoing radiotherapy, do interventions (transfusion or ESAs) aimed at raising the Hb concentration during radiotherapy affect patient outcomes (e.g. response rate, tumour recurrence or tumour-free survival)?
- **Background question 2** – When should a patient be retested after a transfusion to assess the response, guide if further transfusions are required and avoid over-transfusion?

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin

2.3 Development of evidence statements, recommendations and practice points

For each research question addressed by the systematic review, the body of evidence was consolidated into evidence statements and rated according to the matrix shown in Table 2.1 (below), which considers five domains: evidence base, consistency, clinical impact, generalisability and applicability. For included studies, evidence base and consistency were derived directly from the literature identified for each research question, whereas clinical impact, generalisability and applicability were assessed with guidance from the CRG. To ensure that the best available evidence was used, studies of higher levels of evidence (i.e. Levels I or II) were included in preference to those presenting lower levels of evidence (i.e. Levels III or IV). This minimised the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Evidence statements were only transformed into 'action-oriented' recommendations where:

- the body of evidence was sufficient – that is, wherever the evidence yielded support for recommendations of at least NHMRC Grade C (see Table 2.2, below)
- the question type was interventional – that is, it evaluated the effectiveness of an intervention.

The recommendations were carefully worded to reflect the strength of the body of evidence.

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation, the CRG developed practice points through a consensus-based process, to guide clinical practice.

For prognostic and aetiological questions, the evidence base provided only an indication of the risk associated with a particular factor; thus, it was not possible to make an evidence-based recommendation for a change in practice. Instead, the CRG's consensus-based process (used to develop practice points to guide practice) was informed by the prognostic and aetiologic review, and by clinical experience.

Table 2.1 Body of evidence matrix

COMPONENT	A (✓✓✓)	B (✓✓)	C (✓)	D (X)
	Excellent	Good	Satisfactory	Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I – III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence are different to the target population, but it is clinically sensible to apply this evidence to the target population for the guideline	Population/s studied in the body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population for the guideline
Applicability	Directly applicable to the Australian health-care context	Applicable to the Australian health-care context, with a few caveats	Probably applicable to the Australian health-care context, with some caveats	Not applicable to the Australian health-care context

Source: NHMRC 2009¹⁴

Table 2.2 Definitions of NHMRC grades for recommendations

Grade	Definition
GRADE A	Body of evidence can be trusted to guide practice
GRADE B	Body of evidence can be trusted to guide practice in most situations
GRADE C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
GRADE D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC 2009¹⁴

ARCHIVED

3 Clinical guidance

This chapter provides clinical guidance in the form of recommendations (based on evidence) and practice points (based on CRG consensus). The guidance is organised around the six questions that formed the basis of the systematic review. Full details of the findings of the systematic review are given in the accompanying technical report.

The search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically. The experience of many clinicians working with Aboriginal and Torres Strait Islander communities suggests a high rate of anaemia. This has particularly influenced their care of children and pregnant women. As has been noted in the past, there is a paucity of population evidence regarding the prevalence and aetiology of anaemia in Aboriginal and Torres Strait Islander populations. Given the burden of disease carried by these populations, research in this area is overdue and Aboriginal communities may wish to initiate research that could help ensure that the urgent need to provide high quality, targeted care is better informed.

3.1 Effect of anaemia on outcomes

Question 1 (Aetiological question)

In medical patients, is anaemia an independent risk factor for adverse outcomes?

Anaemia as defined by the World Health Organization (WHO) is a haemoglobin (Hb) level of ≤ 130 g/L in males and ≤ 120 g/L in females. It has been assumed that patients with coronary, cerebrovascular or respiratory diseases, or even the elderly, tolerate anaemia poorly, and therefore suffer from increased morbidity and perhaps mortality. This has led to higher Hb levels being used for transfusion in these patient populations. The 2001 NHMRC/ASBT guidelines identified gaps in knowledge about anaemia in such patient populations.¹ The aim of this question was to establish whether anaemia is an independent risk factor for adverse outcomes.

The population groups prespecified as essential for the review were acute coronary syndrome (ACS) and the elderly. Heart failure, cancer and renal patients were also included because systematic reviews of these populations had already been published.

The findings of the review indicate whether anaemia is an independent risk factor for adverse outcomes. However, they do not prove that anaemia causes these outcomes or that correction of the anaemia will reverse the outcomes.

3.1.1 Acute coronary syndrome

EVIDENCE STATEMENTS – acute coronary syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.1	In patients with ACS, anaemia is independently associated with all-cause mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.2	In patients with ACS, the effect of anaemia on cardiovascular mortality is uncertain.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.3	In patients with NSTEMI-ACS, anaemia is independently associated with MI and recurrent ischaemia.	✓✓	NA	✓✓	✓✓✓	✓✓

ACS, acute coronary syndrome; ES, evidence statement; MI, myocardial infarction; NSTEMI-ACS, non-ST segment elevation acute coronary syndrome

✓✓✓=A; ✓✓=B; **NA**, not applicable (see Table 2.1)

Twelve prospective cohort studies (Level II) were included for the ACS population; 10 provided evidence for mortality,¹⁵⁻²⁴ and 4 for composite or cardiovascular outcomes.^{21,22,25,26}

A fair-quality study showed that anaemia, as defined by WHO, was an independent risk factor for all-cause mortality and death due to progressive heart failure in patients diagnosed with acute myocardial infarction (MI), but was not an independent risk factor for sudden cardiac death.¹⁵ In a study by Valeur et al, WHO-defined anaemia was an independent risk factor for mortality in patients with ACS with heart failure only.¹⁶ This study also showed that a one standard deviation increase in Hb resulted in a significantly decreased risk of all-cause mortality (12% reduction) and death due to progressive heart failure (20% reduction). Most of the analyses showed that Hb concentrations below 150 – 160 g/L were a significant independent risk factor for 30-day mortality.¹⁶ In addition, a 10 g/L decrease in Hb significantly increased the risk of mortality.

In summary, the results were generally consistent across all included studies, with most suggesting that anaemia is an independent risk factor for mortality and adverse cardiovascular outcomes. Evidence from one large good-quality study suggests that any decrease in baseline Hb concentration is associated with an increased risk of mortality.¹⁹

3.1.2 Heart failure

EVIDENCE STATEMENTS – heart failure

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.4	In patients with heart failure, anaemia is independently associated with mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.5	In patients with heart failure, anaemia may be independently associated with reduced functional or performance status and quality of life.	✓✓	NA	X	✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; X=D; NA, not applicable (see Table 2.1)

The literature search identified three systematic reviews (which did not strictly meet the requirements for Level I evidence, and were therefore not formally included in the review) and 15 prospective cohort studies (Level II evidence). Fourteen studies provided evidence for mortality^{15,27-39} and one study provided evidence for functional or performance status or quality of life.⁴⁰

All included studies showed that anaemia (as defined by WHO) was associated with an increased risk of all-cause mortality. The association was particularly strong for studies with more than 1 year of follow-up, with four fair to good-quality studies showing increased risks of mortality of 21 – 47%.^{15,27,35,36} Analyses of different Hb concentrations consistently showed that lower Hb concentrations were significantly associated with increased risk of mortality. It was not obvious whether the increased mortality was due to specific cardiovascular events.

One good-quality study assessed the association between various Hb concentrations and functional or performance status using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).⁴⁰ The study found that low Hb is an independent risk factor for reduced quality of life.

3.1.3 Community-dwelling elderly

EVIDENCE STATEMENTS – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.6	In a community-dwelling elderly population, anaemia is independently associated with mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓
ES1.7	In a community-dwelling elderly population, anaemia may be independently associated with reduced functional or performance status and quality of life.	✓✓	✓✓	X	✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; X=D; NA, not applicable (see Table 2.1)

For the purposes of the systematic review, the population 'community-dwelling elderly' was defined as those aged >65 years who were community dwelling and had no significant morbidity. The review identified no Level I evidence and 12 prospective cohort studies (Level II) for this population.⁴¹⁻⁵¹

Four fair-quality studies of subjects aged ≥ 65 years found that anaemia was independently associated with mortality.^{42,45,49,51} One of these studies also found that, although anaemia was independently associated with all-cause and non-cardiovascular mortality, it was not an independent predictor of cardiovascular mortality.⁵¹ Additional studies assessing different Hb concentrations consistently showed that low Hb was associated with increased mortality.^{41-43,46,48}

The findings suggest that anaemia is an independent risk factor for mortality in the elderly community-dwelling population, but not necessarily due to cardiac events. In relation to quality of life, two studies (fair to good quality) suggest that anaemia is associated with decreased quality of life.^{50,52}

3.1.4 Cancer

EVIDENCE STATEMENTS – cancer		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.8	In patients with cancer, anaemia is independently associated with mortality.	✓✓	✓	✓	✓✓	✓✓✓
ES1.9	In patients with cancer, the effect of anaemia on functional or performance status and quality of life is uncertain.	✓	✓	X	✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

The review identified four systematic reviews that did not strictly meet the criteria for Level I evidence and were therefore not formally included in the review. Thirteen prospective cohort studies (Level II) were identified, conducted in subjects with a range of different types of cancer including prostate cancer, breast cancer, lung cancer, colorectal cancer, renal cancer and multiple myeloma.⁵³⁻⁶⁵

One good-quality study found a significant association between anaemia (as defined by WHO) and post-progression survival in 640 men with metastatic prostate cancer.⁵³

Ten studies of poor to fair quality examined the relationship between different Hb concentrations and mortality. Seven of these studies showed a significant relationship between low Hb and an increase in mortality or a reduction in survival.^{54-57,59,60,62} Overall, the results of these studies suggest that anaemia or low Hb is associated with decreased survival.

Two poor-quality studies examined the relationship between lower Hb and quality of life using two quality-of-life instruments: the Short Form-36 (SF-36) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (QLQ-C30).^{51,65} The results suggest an association between low Hb and quality of life; however, due to the poor quality of these studies, this relationship remains uncertain.

3.1.5 Renal

EVIDENCE STATEMENTS – chronic kidney disease

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.10	In patients with CKD (including dialysis patients), anaemia is independently associated with all-cause or cardiovascular mortality.	✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.11	In adults with CKD, anaemia is independently associated with stroke.	✓	NA	✓✓	✓✓	✓✓
ES1.12	In patients with CKD (including dialysis patients), Hb concentration is associated with reduced quality of life.	✓	✓✓	✓	✓✓✓	✓✓

CKD, chronic kidney disease; ES, evidence statement; Hb, haemoglobin

✓✓✓=A; ✓✓=B; ✓=C; NA, not applicable (see Table 2.1)

One systematic review was identified that did not strictly meet the definition of a Level I study because it included both prospective and retrospective cohort studies.⁶⁶ The review concluded that studies consistently show an association between reduced Hb and increased mortality. The review also identified 15 prospective cohort studies (Level II), mainly of fair quality, that included patients predialysis and on dialysis.⁶⁷⁻⁸¹ Eight fair to good-quality prospective cohort studies showed the relationship between different Hb concentrations and mortality.^{68,69,71,72,74,75,77,79} These studies consistently showed that anaemia is independently associated with all-cause or cardiovascular mortality, with lower Hb concentrations increasing the risk of mortality up to two-fold. There was also evidence from one fair-quality prospective cohort study that anaemia was an independent risk factor for stroke.⁶⁷

Six fair to poor-quality prospective cohort studies assessed quality of life using the SF-36.^{70,73,76,78,80,81} These studies concluded that higher Hb concentrations are independently associated with improved quality of life in both predialysis and dialysis patients.

3.2 Effect of red blood cell transfusion on outcomes

Question 2 (Interventional question)

In medical patients, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

Patients are transfused to treat symptoms, reduce morbidity and mortality, and improve their quality of life. The literature review aimed to establish whether receiving a transfusion affects patient outcomes. The review examined the effect of red blood cell (RBC) transfusions in a general population of medical patients, and in subsets of patients in whom a different management strategy might be appropriate. These subsets included patients with ACS, heart failure, cancer or upper gastrointestinal blood loss.

The evidence included some studies comparing restrictive and liberal transfusion strategies, and some observational studies comparing outcomes in patients receiving transfusion to patients who were not transfused. The review included only those studies that had at least 500 subjects, and that adjusted for potential confounding variables using multivariate analysis.

3.2.1 Medical population

EVIDENCE STATEMENTS – medical population		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.1	In medical patients, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.	✓	✓✓	X	✓	✓✓

ES, evidence statement; RBC, red blood cell

✓✓=B; ✓=C; X=D; (see Table 2.1)

PRACTICE POINTS – medical population

PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell

For the comparison of restrictive and liberal transfusion strategies in general medical patients, a Cochrane review by Carless et al (Level I) was identified.⁶² The review assessed data from 17 randomised controlled trials (RCTs) including mainly surgical, critical care and paediatric patients. Studies varied in their definition of restrictive and liberal policies. No difference in mortality or rate of stroke or thromboembolism was identified, but there was a reduction in in-hospital mortality, infection and cardiac events among patients transfused using a restrictive policy. As these findings were largely based on surgical patients, their generalisability to the medical population is limited.

In the absence of direct evidence to support recommendations for the general medical population, evidence from other patient groups was applied to derive a series of practice points. Decisions on whether to transfuse should take into account the absence of proven benefit, and should follow a precautionary principle. In medical patients, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.

The Caring for Australasians with Renal Impairment (CARI) guidelines provide recommendations for the management of anaemia in patients with chronic kidney disease (CKD);⁶³ while the *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* are appropriate for patients with decompensated upper gastrointestinal bleeding.⁴ Practice points and recommendations for other

specific medical populations – for example, ACS, heart failure, cancer and acute upper gastrointestinal blood loss – are presented in the following sections. In addition, advice relating to the management of chronically transfused patients (including patients with thalassaemia and myelodysplasia) is presented under Question 6.

3.2.2 Acute coronary syndrome

EVIDENCE STATEMENTS – acute coronary syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.2	In ACS patients with a Hb concentration >100 g/L, RBC transfusion may be associated with a higher risk of mortality, proportional to Hb concentration.	✓	✓✓	✓✓	✓✓✓	✓✓✓
ES2.3	In ACS patients with an <i>admission</i> Hb concentration <100 g/L, RBC transfusion may be associated with a lower risk of mortality.	X	✓✓	✓	✓✓✓	✓
ES2.4	In ACS patients with a <i>nadir</i> Hb concentration <80 g/L, RBC transfusion may be associated with a lower risk of mortality.	✓	✓✓	X	✓✓✓	✓✓✓
ES2.5	In ACS patients with a <i>nadir</i> Hb concentration of 80 – 100 g/L, RBC transfusion is not associated with an altered mortality risk.	✓	✓✓	NA	✓✓✓	✓✓✓
ES2.6	In patients with ACS, RBC transfusion may be associated with an increased risk of recurrence (up to 6 months) of MI.	✓	NA	✓✓	✓✓	✓✓✓

ACS, acute coronary syndrome; ES, evidence statement; Hb, haemoglobin; MI, myocardial infarction; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

RECOMMENDATION – acute coronary syndrome

R1

GRADE C

In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.

PRACTICE POINTS – acute coronary syndrome

PP5

In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. (See PP1 and PP2).

PP6

In patients with ACS and a Hb concentration of 80 – 100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits. (See PP1 and PP2).

ACS, acute coronary syndrome; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell

In patients with ACS, four retrospective cohort studies (Level III-2) assessed the relationship between mortality and transfusion at varying Hb concentrations.^{21,84-86} Although the included studies analysed the data using a range of haematocrit or Hb categories, the results have been consolidated into specific Hb ranges to best inform clinical practice. The results of these studies consistently indicate that in ACS patients with a Hb concentration >100 g/L, RBC transfusion may be associated with a higher risk of mortality, proportional to Hb concentration. In ACS patients with a Hb concentration of 80–100 g/L, RBC transfusion is not associated with an altered mortality risk, and may be associated with an increased risk of recurrence of MI.

In patients with a Hb concentration of <80 g/L, the association between RBC transfusion and mortality is less clear. The results of Wu⁸⁶ and Sabatine²¹ showed reduced mortality in patients receiving transfusions at lower admission Hb concentrations; however, the studies by Rao⁸⁷ and Alexander⁸⁴ found that transfusion at lower nadir Hb concentrations was not associated with reduced mortality. The CRG considered that nadir Hb may be more relevant than admission Hb for clinical decision making.

An additional study by Shishehbor⁸⁸ reported that, in patients with ACS, RBC transfusion may be associated with an increased risk of recurrence of MI.

3.2.3 Heart failure

EVIDENCE STATEMENTS – heart failure

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.7	In patients with heart failure, the effect of RBC transfusion on the risk of mortality is uncertain.	✓	NA	NA	✓✓	✓✓

ES, evidence statement; RBC, red blood cell

✓✓=B; ✓=C; NA, not applicable (see Table 2.1)

PRACTICE POINT – heart failure

PP7

In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status. For further guidance on how to manage patients with heart failure, refer to general medical or ACS sections, as appropriate (R1, R3, PP3–PP6).

ACS, acute coronary syndrome; PP, practice point; R, recommendation; RBC, red blood cell

In patients with heart failure, the results of one fair-quality prospective cohort study (Level III-2)⁸⁹ showed that RBC transfusion was significantly associated with a reduction in 30-day mortality and may be associated with reduced in-hospital mortality. However, because of the low level of evidence, this relationship remains uncertain.

In the absence of strong evidence, guidance relating to transfusion policies in this patient group can be found in the practice point made by the CRG, and extrapolated from experience in other patient populations.

Because of the risk of circulatory overload, patients with heart failure should be transfused with caution, with clinical assessment between each transfused unit.

3.2.4 Cancer

EVIDENCE STATEMENTS – cancer		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.8	In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital mortality.	✓	NA	✓	✓✓✓	✓✓
ES2.9	In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital venous and arterial thromboembolic events.	✓	NA	✓	✓✓✓	✓✓

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; **NA**, not applicable (see Table 2.1)

PRACTICE POINTS – cancer	
PP8	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.
PP9	There is a lack of specific evidence relating to the effects of RBC transfusion in patients with cancer. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia. When treating patients with cancer, refer also to the general medical population PP1–PP4.

PP, practice point; RBC, red blood cell

A single fair-quality retrospective cohort study (Level III-2) reported an increased risk of mortality and of venous and arterial thrombotic events in transfused hospitalised patients with cancer.⁹⁰ This study provides insufficient evidence on which to base evidence-based recommendations.

In the absence of strong evidence, guidance relating to transfusion policies in this patient group can be found in practice points made by the CRG, and extrapolated from experience in other patient populations.

3.2.5 Acute upper gastrointestinal blood loss

EVIDENCE STATEMENTS – acute upper gastrointestinal blood loss		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.10	In patients with acute upper gastrointestinal blood loss, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.	X	NA	NA	✓✓✓	X
ES2.11	In patients with acute upper gastrointestinal blood loss, the effect of RBC transfusion on mortality is uncertain.	✓	NA	NA	✓✓✓	✓

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓=C; X=D; NA, not applicable (see Table 2.1)

PRACTICE POINTS – acute upper gastrointestinal blood loss

PP10	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. Therefore, a more restrictive approach may be appropriate. There are no data to support a specific Hb treatment target in these patients.
PP11	For critically bleeding patients, refer to <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion</i> (2011). ⁴

Hb, haemoglobin; PP, practice point

A poor-quality RCT (Level II)⁹¹ assessed the effect of RBC transfusion on mortality. The study was underpowered to detect differences in the treatment arms; however, the transfused group experienced significantly higher rates of rebleeding. A good-quality prospective cohort study (Level III-2)⁹² assessed the risk of mortality relating to early RBC transfusion in patients with acute upper gastrointestinal haemorrhage. These results demonstrated no significant association between RBC transfusion and mortality.

In the absence of strong evidence, guidance relating to transfusion policies in this patient group can be found in practice points made by the CRG, and extrapolated from experience in other patient populations.

3.3 Effect of erythropoiesis - stimulating agents and iron

Question 3 (Interventional question)

In medical patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion?

Hb, haemoglobin; RBC, red blood cell

The transfusion of RBCs is resource intensive, and has been associated with short and long-term morbidity in recipients. Recombinant erythropoiesis-stimulating agents (ESAs) promote bone marrow production of RBCs. However, ESAs have been associated with complications of therapy in some patients, particularly where the baseline Hb is near normal. In some patients, iron administration may also be effective. The systematic review examined the effectiveness of ESAs or iron supplementation in subgroups of anaemic patients.

Erythropoietin is secreted by the kidneys in response to hypoxia and stimulates erythropoiesis in the marrow. A reduction in renal mass may contribute to reduced erythropoietin levels, and therefore anaemia. ESAs are synthetic molecules that replicate this function. They are effective in increasing the Hb in individuals with severely impaired renal function, but have also been used to overcome reduced erythropoiesis due to a variety of other causes; these include cancer, haematological malignancies and other chronic diseases. The erythropoietic response to ESAs is reduced in primary bone marrow disorders and where chronic inflammation contributes to anaemia.

The effectiveness of ESAs in treating anaemia and their consequent potential effect on functional status must be balanced against risks associated with therapy; both the effectiveness and the risks vary in different diagnostic subgroups.

Iron deficiency results when iron losses or requirements exceed absorption; it is often multifactorial, and may be absolute or relative. Relative iron deficiency is commonly referred to as functional iron deficiency (FID). A patient with FID has adequate stores of iron, but the iron cannot be mobilised for erythropoiesis, which is mediated by elevated hepcidin. FID is commonly seen in patients with end-stage kidney disease, but may also contribute to anaemia in patients with inflammatory diseases, chronic heart failure (CHF) and cancer.

The serum ferritin level is the most readily available and useful index of iron deficiency.⁹³ In an adult with anaemia, a ferritin level below 15 mcg/L is diagnostic of iron deficiency, and levels of 15 – 30 mcg/L are highly suggestive of the condition. However, ferritin is also an acute-phase protein and is elevated in inflammation, infection, liver disease and malignancy. This can result in misleadingly high ferritin levels in iron-deficient patients with coexisting systemic illness.

Iron therapy may be used as a primary treatment for anaemic or nonanaemic iron deficiency, or to augment the response to ESAs. When administered with ESAs, iron therapy prevents both absolute iron deficiency and FID, and minimises the dose of ESA needed to achieve target Hb concentrations.

3.3.1 Cancer

EVIDENCE STATEMENTS – cancer (erythropoiesis-stimulating agents)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.1	In anaemic adults with cancer, ESA therapy increases the risk of all-cause mortality; this effect appears to be greater in patients with a Hb concentration > 100 g/L.	✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓
ES3.2	In adult cancer patients with non chemotherapy-induced anaemia, ESA therapy increases the risk of all-cause mortality.	✓✓	✓✓✓	✓✓	✓✓✓	✓✓✓
ES3.3	In adult cancer patients with chemotherapy-induced anaemia, the effect of ESA therapy on mortality is uncertain.	✓✓	✓✓✓	X	✓✓✓	✓✓✓
ES3.4	In anaemic adults with cancer, ESA therapy reduces transfusion incidence and volume.	✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES3.5	In anaemic adults with cancer, ESA therapy increases the risk of thromboembolic events.	✓✓	✓✓✓	✓✓	✓✓✓	✓✓
ES3.6	In anaemic adults with cancer, ESA therapy may improve functional or performance status; however, the magnitude of this effect appears slight.	✓	✓	X	✓✓✓	✓✓

EVIDENCE STATEMENTS – cancer (iron therapy)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.7	In anaemic adults with cancer receiving ESAs, the effect of IV iron versus oral or no iron on short-term mortality is uncertain.	✓✓	✓✓	NA	✓✓	✓✓
ES3.8	In adults with cancer-related anaemia receiving ESAs, IV iron may reduce the incidence of RBC transfusion.	✓✓	✓✓	✓	✓✓	✓
ES3.9	In anaemic patients with gynaecological cancer receiving chemotherapy, IV iron may reduce the incidence and volume of RBC transfusion.	✓	NA	✓✓	✓✓✓	✓
ES3.10	In adults with chemotherapy-induced anaemia receiving ESAs, the effect of IV iron versus oral or no iron on the incidence of thromboembolic events is uncertain.	✓✓	✓✓	NA	✓✓	✓
ES3.11	In adults with non-myeloid malignancies and chemotherapy-induced anaemia receiving ESAs, IV iron versus oral or no iron appears to have no effect on functional or performance status.	✓	NA	NA	✓✓	✓
ES3.12	In anaemic patients with gynaecological cancer receiving chemotherapy, the effect of IV iron versus oral iron on functional or performance status is uncertain.	✓	NA	NA	✓✓✓	✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

RECOMMENDATION – cancer

R2

GRADE A

In cancer patients with anaemia, the *routine* use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.

PRACTICE POINTS – cancer

PP8^a

In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.

PP12

In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.

^a Repeated from Section 3.2.4, above

ESA, erythropoiesis-stimulating agent; PP, practice point; R, recommendation

Erythropoiesis-stimulating agents – cancer

In patients with cancer, anaemia may be due to inflammation, chemotherapy, bone marrow infiltration by malignancy or haematinic deficiency (e.g. iron deficiency). Patients with haematological malignancies form a separate subgroup, because they have potentially defective erythropoiesis and therefore a reduced capacity to respond to ESAs.

A systematic review of RCTs (Level I)⁹⁴ evaluated the effectiveness of ESAs in individuals with nonhaematological malignancies. The study documented a significant increase in the risk of mortality with ESA treatment among cancer patients; this was confirmed by a meta-analysis that included five studies published subsequently. There was a nonsignificant trend towards a higher risk of mortality among patients with higher baseline Hb who received ESA treatment.

Meta-analyses of the studies from Tonelli et al⁹⁴ and two fair-to-poor-quality RCTs (Level II)^{95,96} identified benefits in patients with cancer receiving ESAs. There was a significantly lower likelihood of transfusion among patients treated with ESAs if the baseline Hb was 120 g/L or lower; in addition, the mean RBC transfusion volume among all patients who received ESAs was 0.8 units less than in untreated patients. There was a favourable effect on functional or performance status. However, a meta-analysis of studies – including those identified by Bohlius et al,⁹⁷ Tonelli et al,⁹⁴ Hoskin⁹⁵ and Tsuboi⁹⁶ – found an increased risk of thromboembolic events among cancer patients treated with ESAs.

Based on these analyses, it is not possible to draw conclusions for patients with specific cancer subtypes; it is also not possible to distinguish between patients with different pretransfusion Hb concentrations, or between patients being treated with curative rather than palliative intent. In view of the increased mortality and incidence of thromboembolic events among cancer patients treated with ESAs, decision making should be individualised in patients with cancer. ESAs are not currently listed on the Pharmaceutical Benefits Scheme (PBS) for reimbursement for patients with cancer.

Intravenous iron – cancer

The literature review identified five RCTs (Level II) that evaluated the use of iron therapy in anaemic patients with cancer. All of the studies compared intravenous (IV) iron with either oral iron or no iron therapy. Participants received adjuvant darbepoetin in three of the studies, which were of fair or good quality,⁹⁸⁻¹⁰⁰ and adjuvant erythropoietin in one study,¹⁰¹ which was of poor quality.

Of the four RCTs that reported mortality,⁹⁸⁻¹⁰¹ no significant difference was found in patients treated with IV iron compared to patients who received oral or no iron therapy; however, the studies were underpowered. No significant difference was found after meta-analysis.

Two studies^{99,102} found that, compared with patients who did not receive IV iron, patients treated with IV iron had both a significantly lower incidence and median volume of RBC transfusion. There was no significant difference in functional status (Functional Assessment of Cancer Therapy (FACT) score) between the groups in both studies. One of these studies¹⁰² compared IV iron alone to oral iron in gynaecologic cancer patients with anaemia (Hb <100 g/L) who underwent primary surgery and were receiving platinum-based chemotherapy.

Of the three studies reporting thromboembolic events, there was no significant difference between patients treated with darbepoetin plus IV iron and those treated with darbepoetin plus oral iron or no iron, including after meta-analysis.⁹⁸⁻¹⁰⁰

Risks associated with ESAs include increased mortality, venous thromboembolism, tumour progression and stroke. With the growing awareness of these risks, the role of iron therapy (alone or in combination with lower doses of ESAs) in selected patients requires further study. While iron therapy is generally recommended to augment the response in ESA recipients with iron deficiency, there is insufficient evidence to recommend the routine use of IV iron. Patients with cancer and anaemia should be evaluated and treated for iron deficiency before ESAs are initiated; these patients should be re-evaluated periodically during the course of therapy. IV iron may be required when oral administration is not possible or is ineffective.

3.3.2 Chronic heart failure

EVIDENCE STATEMENTS – chronic heart failure (erythropoiesis-stimulating agents)

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.13	In anaemic patients with CHF, the effect of ESAs on mortality is uncertain.	✓✓✓	X	X	✓✓	✓✓✓
ES3.14	In anaemic patients with CHF, the effect of ESAs on transfusion requirements is uncertain.	X	NA	X	X	✓✓
ES3.15	In anaemic patients with CHF, the effect of ESAs on the incidence of thromboembolic events is uncertain.	✓✓✓	✓✓	NA	✓	✓✓
ES3.16	In anaemic patients with CHF, ESAs may improve functional or performance status compared with no ESAs.	✓✓✓	✓	✓	✓	✓✓

EVIDENCE STATEMENTS – chronic heart failure (iron therapy)

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.17	In CHF patients with iron deficiency, the effect of IV iron on mortality is uncertain.	✓✓	✓✓	NA	✓✓	✓✓
ES3.18	In CHF patients (NYHA functional classes II or III) with iron deficiency (absolute and functional), IV iron improves functional or performance status, independent of Hb concentration.	✓✓	✓✓	✓✓	✓✓	✓✓

CHF, chronic heart failure; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

RECOMMENDATION – chronic heart failure

R3

GRADE B

In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status.

This is consistent with the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006*.²

Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.

CHF, chronic heart failure; IV, intravenous; NYHA, New York Heart Association; R, recommendation

Erythropoiesis-stimulating agents – chronic heart failure

One systematic review (Level I), which included a large subset of patients with diabetes and congestive cardiac failure, found that ESA therapy was associated with reduced mortality.¹⁰³ In a separate systematic review, the incidence of thromboembolic events, mortality and heart failure-related hospitalisations were not affected by ESAs,¹⁰⁴ but there was a significant improvement in exercise tolerance. ESAs are not currently listed on the PBS for reimbursement for patients with cardiac failure.

Intravenous iron – chronic heart failure

Iron deficiency is common in patients with CHF, and is usually associated with anaemia.

Two RCTs (Level II), one of good quality¹⁵ and one of poor quality,¹⁰⁵ evaluated the use of IV iron therapy in patients with CHF (New York Heart Association (NYHA) class II or III). Both studies included anaemic and nonanaemic patients who were likely to have either absolute iron deficiency (ferritin <100 mcg/L) or FID (ferritin 100–300 mcg/L with a transferrin saturation of 20%).

There was no significant difference in mortality between patients treated with IV iron and patients who did not receive IV iron, including after meta-analysis; however, the studies were underpowered. Neither study reported the incidence or volume of blood transfusion. Both studies showed a significant improvement in NYHA classification with IV iron.

The good-quality, multicentre RCT by Anker et al included CHF patients with absolute iron deficiency and FID, with Hb concentrations of 95–135 g/L.¹⁵ The study demonstrated reduced symptoms and improved submaximal exercise tolerance and quality of life with use of IV ferric carboxymaltose compared to a placebo. Improvements were independent of Hb concentrations. There was no significant difference between IV iron and the placebo in the rates of hospitalisation for any cardiovascular cause or for vascular disorders.

It is important to look for and treat iron deficiency in patients with CHF to reduce symptoms and improve exercise tolerance and quality of life. This advice has been incorporated as a Grade B recommendation in the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia*, from the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.

3.3.3 Chronic kidney disease

EVIDENCE STATEMENTS – chronic kidney disease (erythropoiesis-stimulating agents)

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.19	In anaemic patients with CKD, the effect of ESA therapy to a Hb target of 100 – 110 g/L on mortality is uncertain compared with no ESA therapy.	✓✓	✓✓✓	NA	✓✓	✓✓✓
ES3.20	In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignant condition at baseline, ESAs increase the incidence of mortality attributable to cancer.	✓✓	NA	✓✓✓	✓✓✓	✓✓✓
ES3.21	In anaemic patients with CKD, ESA therapy to a Hb target of 100 – 110 g/L reduces RBC transfusion incidence compared with no ESA therapy.	✓✓	✓✓	✓✓✓	✓✓	✓✓✓
ES3.22	In anaemic patients with CKD, targeting a Hb concentration above 130 g/L with ESA therapy increases the incidence of stroke and other thromboembolic events. The effect of targeting lower Hb concentrations is uncertain.	✓✓	✓✓	✓✓	✓✓	✓✓✓
ES3.23	In anaemic patients with CKD, ESA therapy to a Hb target of 100 – 110 g/L does not appear to affect the incidence of MI.	✓✓	✓✓	✓✓	✓✓	✓✓✓
ES3.24	In nondiabetic dialysis patients, compared to no treatment, ESA therapy targeted to a Hb ≥95 g/L may reduce fatigue and improve physical functioning.	✓✓	✓	✓	✓✓	✓✓✓
ES3.25	In anaemic patients with non dialysis-dependent CKD, ESA therapy to a Hb target of 100 – 110 g/L may reduce fatigue, but has little impact on physical functioning.	✓✓	✓	✓	✓✓	✓✓✓

EVIDENCE STATEMENTS – chronic kidney disease (iron therapy)

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.26	In anaemic patients with CKD receiving ESAs, the effect of IV iron on mortality is uncertain.	✓	✓✓	NA	✓✓	✓✓
ES3.27	In anaemic patients with CKD on dialysis and receiving ESAs, IV iron may reduce the need for an anaemia intervention. ^a	X	NA	✓	✓✓✓	✓✓
ES3.28	In anaemic patients with non dialysis-dependent CKD, the effect of IV iron on RBC transfusion requirement is uncertain.	X	NA	X	✓✓	✓✓
ES3.29	In anaemic patients with non dialysis-dependent CKD, IV iron therapy may improve functional or performance status compared to oral iron therapy.	✓✓	✓	X	✓✓	✓✓

CKD, chronic kidney disease; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; MI, myocardial infarction; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

^a Anaemia intervention was defined as either an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study.

RECOMMENDATIONS – chronic kidney disease

R4

GRADE B

In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient.

Note: The CARL guidelines recommend a Hb target between 100–115 g/L⁵

R5

GRADE C

In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to relieve fatigue, after consideration of risks and benefits for the individual patient.

Note: The CARL guidelines recommend a Hb target between 100–115 g/L⁵

R6

GRADE B

In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.

R7

GRADE B

In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the routine use of ESAs is not recommended because of the increased risk of cancer-related mortality.

PRACTICE POINTS – chronic kidney disease

PP13

ESA use is less effective in patients with chronic renal failure who have absolute or functional iron deficiency.

PP14

For comprehensive information about ESA and iron therapy in patients with CKD, refer to CARl iron guidelines.⁵

CARl, Caring for Australasians with Renal Impairment; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell

Erythropoiesis-stimulating agents – chronic kidney disease

The literature review identified four systematic reviews (Level I) of the use of ESAs for anaemic patients with CKD.^{106–109} Only reviews that compared ESAs with no ESA treatment were eligible for inclusion. Therefore, Strippoli et al, which compared Hb targets, rather than treatment with no treatment, was excluded.¹¹⁰ Similarly, when discussing the results from Tonelli et al, only the studies defined by the review as comparing ESA with no ESA, rather than comparing high with intermediate or low target Hb protocols, were eligible for inclusion.¹⁰⁷

A significantly lower incidence of cardiovascular mortality, but not overall mortality, has been identified in patients with CKD treated with ESAs.¹⁰⁷ Increased mortality in ESA-treated CKD patients with a history of malignancy has been reported.¹¹¹ In addition, a significant increase in MI, stroke and other thromboembolic events has been found in diabetic patients with CKD.¹¹²

The incidence of RBC transfusion in patients with non dialysis-dependent CKD¹⁰⁸ and patients on haemodialysis¹⁰⁷ is reduced with ESAs, and the quality of life in dialysed patients is improved with ESAs.^{113,114} Although non dialysis-dependent CKD patients with diabetes had an improved score on the FACT-fatigue test, there were no significant differences in energy and functioning scores and severity of cardiac failure in those who received ESAs.^{111,112,115}

These findings suggest that ESAs can be used to reduce the incidence of RBC transfusion in patients with non dialysis-dependent CKD and in CKD dialysis patients. ESA use can also result in an improved quality of life in dialysed and non dialysis-dependent CKD patients with diabetes. However, in view of the increased risk of MI, stroke and other thromboembolic events in some patients, ESAs should be used with caution in this population. The United States Food and Drug Administration has highlighted an increased risk for patients with a target Hb of >140 g/L. An appropriate target Hb for ESA therapy has not been defined in patients with CKD, but caution is recommended in patients with a Hb >100 g/L.

Intravenous iron – chronic kidney disease

The literature review identified one systematic review (Level I)¹¹⁶ and five RCTs (Level II) of the use of IV iron for anaemic patients with CKD.

The systematic review¹¹⁶ compared the use of IV versus oral iron in anaemic patients with CKD (stages III to V). This review included studies assessing iron therapy in patients with non dialysis-dependent CKD and CKD dialysis patients, with or without ESA treatment.

Two RCTs reported mortality as an outcome, but found no significant difference, including after meta-analysis.^{117,118} No studies reported transfusion incidence. Two RCTs reported the proportion of patients requiring an anaemia intervention (i.e. increase in ESA dose, initiation of non-protocol IV iron or RBC transfusion).^{119,120} One of these RCTs found no significant difference in the need for an anaemia intervention with IV iron (compared to oral iron);¹¹⁹ however, the other RCT found a significant difference with IV iron compared with no iron.¹²⁰

Meta-analysis of the data from the two studies of patients who required an anaemia intervention did not show a significant difference in the mortality rates of CKD patients treated with IV iron, or with oral or no iron therapy.^{119,120}

None of the included studies reported the incidence of thromboembolic events.

Two of the included RCTs^{119,121} reported on functional or performance status. One of these studies¹²¹ showed an improvement. Patients treated with IV iron experienced significantly greater improvements in two measures of quality of life (Symptoms and Effects of CKD on Kidney Disease Quality of Life Questionnaire: KDQoL) than patients treated with oral iron.

3.3.4 Elderly patients

EVIDENCE STATEMENTS – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.30	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on mortality is uncertain.	✓	NA	NA	✓	✓✓
ES3.31	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on thromboembolic events is uncertain.	✓	NA	NA	✓	✓✓
ES3.32	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on functional or performance status is uncertain.	✓	NA	X	✓	✓✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

Erythropoiesis-stimulating agents – elderly patients

A single fair-quality RCT (Level III) of anaemic elderly patients receiving ESAs did not identify an effect on mortality or the incidence of thromboembolic complications.¹²² ESA treatment was associated with functional improvement.

3.3.5 Inflammatory bowel disease

EVIDENCE STATEMENTS – inflammatory bowel disease		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.33	In IBD patients with iron deficiency anaemia, the effect of IV iron versus oral iron on mortality is uncertain.	✓	NA	NA	✓✓	✓✓
ES3.34	In IBD patients with iron deficiency anaemia, it is uncertain whether there is any difference between the effects of IV iron and oral iron on functional or performance status.	✓	NA	X	✓✓	✓✓

ES, evidence statement; IBD, inflammatory bowel disease; IV, intravenous

✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

PRACTICE POINT – inflammatory bowel disease	
PP15	In patients with IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.

IBD, inflammatory bowel disease; IV, intravenous; PP, practice point

Intravenous iron – inflammatory bowel disease

Although anaemia in inflammatory bowel disease (IBD) is multifactorial, iron deficiency and anaemia of chronic disease are common aetiological factors. IV iron therapy is frequently used in IBD patients because oral iron has drawbacks (e.g. intolerance, lack of compliance, poor absorption and worsening of inflammation).

The review identified two RCTs (Level II) that evaluated the use of iron therapy in patients with IBD with iron deficiency anaemia.^{123,124}

Kulnigg et al found no significant difference in mortality between IV and oral iron, but the study was underpowered.¹²³ Neither study reported on the incidence or volume of blood transfusion or thromboembolic events.

In Kulnigg et al, patients treated with IV iron had a greater improvement in SF-36 from baseline at follow-up than patients treated with oral iron.¹²³ In Schroder et al, there were similar improvements from baseline at follow-up for IV iron compared with oral iron for Crohn’s Disease Activity Index, Colitis Activity Index (CAI) and SF-36.¹²⁴ These two studies provided insufficient detail to determine whether the treatment effect on this outcome was statistically significant.

3.3.6 Myelodysplastic syndrome

EVIDENCE STATEMENTS – myelodysplastic syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.35	In anaemic patients with MDS, the effect of ESAs on mortality is uncertain.	X	✓✓	X	✓✓	✓
ES3.36	In anaemic patients with MDS receiving GM-CSF, ESAs may reduce transfusion incidence compared with no ESAs.	X	NA	✓	✓✓	✓✓
ES3.37	In anaemic patients with MDS, the effect of ESAs on thromboembolic events is uncertain.	X	✓✓✓	NA	✓✓	✓
ES3.38	In anaemic patients with MDS, the effect of ESAs on functional or performance status is uncertain.	X	NA	NA	✓✓	✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent; GM-CSF, granulocyte/macrophage colony-stimulating factor; MDS, myelodysplastic syndrome

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

Erythropoiesis-stimulating agents – myelodysplastic syndrome

The review identified three RCTs (Level II)^{125–127} evaluating the use of ESAs in patients with myelodysplastic syndrome (MDS).

MDS is a heterogeneous group of disorders characterised by varying degrees of dyserythropoiesis and marrow infiltration by abnormal haemopoietic cells. There is RCT (Level II) evidence of a favourable impact on mortality among patients with refractory anaemia with ringed sideroblasts (RARS), but not in other MDS subgroups treated with ESAs.¹²⁵

Fewer RBC transfusions were required among patients with MDS when ESAs were added to granulocyte/macrophage colony-stimulating factor (GM-CSF) therapy, provided the baseline endogenous erythropoietin level was ≤500 mU/ml.¹²⁶ No significant differences in the incidence of thromboembolic complications, including stroke, were seen. Patients in whom an erythroid response had been seen at 4 months showed improvements in physical, emotional and functional well-being, fatigue and overall quality of life.¹²⁵

3.3.7 Other populations

The literature review found insufficient evidence to allow recommendations to be made for patients with ACS, cerebrovascular disease and respiratory disease, hepatitis C, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), and for patients undergoing radiotherapy.

3.4 Effect of blood components on outcomes

Question 4 (Interventional)

In medical patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

There is controversy over the benefit of using fresh frozen plasma (FFP), cryoprecipitate and platelet concentrates to improve haemostasis in both procedural and non-procedural settings. The aim of this question was to determine the effect of using such products on mortality, bleeding events and transfusion-related adverse events.

3.4.1 Fresh frozen plasma

EVIDENCE STATEMENTS – fresh frozen plasma		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.1	In patients with acute pancreatitis, the effect of FFP on mortality is uncertain.	X	✓	NA	X	X
ES4.2	In patients with acute pancreatitis, the effect of FFP on bleeding events is uncertain.	X	✓	NA	X	X
ES4.3	In patients with liver disease, the effect of FFP on mortality is uncertain.	X	NA	NA	✓	✓
ES4.4	In patients with liver disease, the effect of FFP on bleeding events is uncertain.	X	NA	NA	X	✓

ES, evidence statement; FFP, fresh frozen plasma

✓=C; X=D; NA, not applicable (see Table 2.1)

PRACTICE POINTS – fresh frozen plasma

PP16

The *routine* use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment.

The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.

PP17

For guidance on the use of FFP in specific patient groups, refer to:

- *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011)⁴
- *Patient Blood Management Guidelines: Module 2 – Perioperative* (2012)⁶
- *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis* (2004)⁷
- AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au)
- *TTP: Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant* (2004).⁸

AHCDO, Australian Haemophilia Centre Directors' Organisation; FFP, fresh frozen plasma; PP, practice point; TTP, thrombotic thrombocytopenic purpura

FFP contains all the coagulation factors and proteins present in normal plasma. FFP is transfused in a range of clinical settings, including critical bleeding/massive transfusion, perioperative, warfarin reversal, liver disease, coagulation factor deficiencies and thrombotic thrombocytopenic purpura (TTP). The literature search identified Level II evidence relating to the use of FFP in two medical populations:

- acute pancreatitis, where FFP has been proposed as a specific therapy to replenish important circulating proteins, particularly the naturally occurring anti-protease system
- liver disease, where FFP is mainly used to replace coagulation factor deficiencies.

The search identified two RCTs (Level II) that compared FFP treatment with no FFP in acute pancreatitis.^{128,129} Neither study found significant differences between the study arms in terms of mortality or gastrointestinal haemorrhage; however, both studies were underpowered to measure the effect of treatment on these outcomes. The search did not find any RCTs reporting the incidence of transfusion-related serious adverse events in patients with acute pancreatitis receiving FFP transfusion.

One poor-quality RCT (Level II) compared FFP treatment with no FFP for patients with liver disease.¹³⁰ The study population comprised 20 patients with liver disease due to paracetamol overdose. The measured coagulation factor levels were significantly higher in the FFP-treated group; however, the study size precluded detection of any clinically or statistically significant differences in mortality or bleeding events between the two groups. The search did not find any RCTs reporting the incidence of transfusion-related serious adverse events in patients with liver disease receiving FFP transfusion.

3.4.2 Fibrinogen and cryoprecipitate

EVIDENCE STATEMENTS – fibrinogen and cryoprecipitate		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.5	In medical patients, no relevant studies were found reporting the effect of fibrinogen replacement, using cryoprecipitate or fibrinogen concentrate on mortality, bleeding events and transfusion-related serious adverse events.	NA	NA	NA	NA	NA

ES, evidence statement; **NA**, not applicable (see Table 2.1)

PRACTICE POINTS – fibrinogen and cryoprecipitate	
PP18	The <i>routine</i> use of cryoprecipitate or fibrinogen concentrate in medical patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified; where transfusion is considered necessary, the risks and benefits should be considered for each patient. Specialist opinion is advised for the management of DIC.
PP19	For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to: ▪ <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion</i> (2011)⁴ ▪ AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) ▪ <i>TTP: Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004).⁸

AHCDO, Australian Haemophilia Centre Directors' Organisation; DIC, disseminated intravascular coagulation; PP, practice point

Cryoprecipitate is prepared from controlled thawing of FFP; it contains factors VIII and XIII, fibrinogen and fibronectin. Some plasma fractionators now produce fibrinogen concentrates, which have the benefits of an improved viral safety profile and a defined dose in a small infusion volume. Fibrinogen concentrate is licensed in Australia for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. There is limited experience with the use of the product in the treatment of congenital dysfibrinogenaemia.

The review did not identify any RCTs (Level II) that assessed the effect of cryoprecipitate or fibrinogen concentrate on outcomes in medical patients. In the absence of evidence, guidance relating to transfusion policies for fibrinogen products can be found in practice points made by the CRG.

3.4.3 Platelet transfusion

EVIDENCE STATEMENTS – platelet transfusion		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.6	In patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on mortality is uncertain.	X	✓✓	✓	✓✓	✓
ES4.7	In patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on bleeding events is uncertain.	X	✓✓	NA	✓	✓
ES4.8	Platelet transfusions are associated with transfusion-related adverse events that can range from mild to serious.	X	✓✓	✓✓	✓✓	✓
ES4.9	In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased mortality, but causation has not been established.	X	NA	✓✓	✓✓	✓✓
ES4.10	In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased risk of thromboembolic events, but causation has not been established.	X	NA	✓	✓✓	✓✓
ES4.11	In patients receiving chemotherapy and prophylactic platelet transfusion, the effect of platelet dose on mortality is uncertain.	✓✓	NA	NA	✓✓✓	✓✓
ES4.12	In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose has no effect on bleeding events defined as mild or greater (WHO grade 2 or above).	✓✓	✓✓	X	✓✓✓	✓✓
ES4.13	In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose does not appear to affect the incidence of transfusion-related adverse events.	✓✓	✓	✓	✓✓✓	✓✓✓

ES, evidence statement; WHO, World Health Organization

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

PRACTICE POINTS – platelet concentrates

PP20

Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.

PP21

In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.⁹

Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness).

Therapeutic platelet transfusions could be considered for treatment of bleeding.

HIT, heparin-induced thrombocytopenia; PP, practice point; TTP, thrombotic thrombocytopenic purpura

Platelet transfusion is a therapeutic intervention used for the prevention and treatment of bleeding in patients with thrombocytopenia or significant platelet dysfunction. The different methods for producing platelets result in differences in the final products (e.g. in dose and risk profile); this should be taken into account when comparing studies. The focus of this systematic review was to first compare prophylactic and therapeutic transfusion strategies, and then compare different platelet transfusion doses.

Prophylactic and therapeutic transfusion strategies

A small number of eligible studies were identified; all involved patients with cancer, including haematological malignancies. Thrombocytopenia was most commonly due to chemotherapy or stem cell transplantation. One additional study was a multivariate analysis of association between transfusions and venous thromboembolism, arterial thromboembolism and mortality in a broad population of hospitalised patients with cancer.⁹⁰ No studies were found that included populations of special interest, such as patients receiving treatment with antifibrinolytic or antiplatelet therapy.

In patients with haematological malignancies receiving chemotherapy, mortality was reported in two studies: an RCT (Level II)¹³¹ that was inadequately powered to detect any clinically or statistically significant differences, and a cohort study (Level IV)¹³² that did not report any comparative data, but reported a mortality rate of 4.3% in patients receiving platelet transfusions.

The cohort study (Level III-2) in a broad population of hospitalised cancer patients⁹⁰ found that platelet transfusion was independently associated with in-hospital mortality, and venous and arterial thromboembolism. This study controlled for a range of variables; however, as a cohort study, it could not establish causality.

Two studies reported the incidence of bleeding events. One RCT (Level II)¹³³ reported no significant difference between study arms, and one cohort study (Level IV)¹³² found an incidence rate of 58.0% for grade 2 bleeding and 5.1% for grade 3–4 bleeding.

Four cohort studies reported the incidence of transfusion-related adverse events in patients receiving platelet transfusions.^{132,134–136} The incidences of adverse events ranged widely between studies. However, these discrepancies can probably be accounted for by differences in the study populations and the type of platelet product transfused.

Platelet transfusion doses

Five RCTs (Level II) assessed platelet dose in patients with haematological malignancies receiving chemotherapy.¹³⁷⁻¹⁴¹ The definitions of thrombocytopenia and the assessed dose ranges varied widely between the studies. Mortality was reported in only one study;¹³⁷ this study found no significant difference between any of the assessed platelet doses, but was underpowered.

Four studies reported the incidence of bleeding events. Slichter et al¹³⁷ and Heddle et al¹³⁸ found no significant difference between study arms in any of the dose comparisons presented. Tinmouth et al found a higher risk of experiencing a minor bleed in patients receiving three platelet units than five platelet units, but no significant difference between different platelet doses for the incidence of major bleeds.¹³⁹ The study by Sensebé et al was underpowered to detect an effect of platelet dose on the incidence of haemorrhage.¹⁴¹

There was no significant difference between study arms in the two studies that reported the incidence of transfusion-related serious adverse events.^{132,137} However, the overall rate of serious adverse events was relatively high in both studies.

3.5 Blood component transfusion

Question 5 (Interventional/Prognostic)

In medical patients, at what INR (PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events?

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time

There is controversy over the benefit of using FFP, cryoprecipitate and platelet concentrates to improve haemostasis in both procedural and non-procedural settings. In the absence of high-quality evidence, clinicians have traditionally relied on laboratory indexes for making decisions about transfusion of these products. The systematic review considered purported 'transfusion-trigger' levels of these various indexes, excluding studies of patients with massive bleeding or requiring warfarin reversal.

Question 5 was originally defined as a prognostic question. It was expected that the best evidence relating to this question would come from large cohort studies that stratified results according to baseline international normalised ratio (INR)/fibrinogen/platelet count. However, the literature search for this module identified a number of highly relevant RCTs that compared different transfusion triggers. Therefore, the CRG decided that this question would be approached initially as an interventional question, and then as a prognostic question if relevant evidence from RCTs was not found. High-quality evidence from RCTs was found for platelet transfusion; hence, this part of the question was treated as an interventional question. In contrast, studies relevant to use of cryoprecipitate and FFP were primarily cohort studies in which patients were stratified by INR, prothrombin time/activated partial thromboplastin time (PT/APTT) or fibrinogen at baseline. Hence, these parts of the question were treated as prognostic questions.

3.5.1 Coagulation parameters and fresh frozen plasma transfusion

EVIDENCE STATEMENTS – coagulation parameters and transfusion		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES5.1	In patients with liver disease, an elevated INR/PT/APTT level is independently associated with an increased risk of mortality.	✓	✓✓	✓✓	✓✓	✓✓
ES5.2	In patients with acute leukaemia, INR/PT/APTT levels may be independently associated with mortality.	✓	NA	✓	✓✓	✓✓
ES5.3	In patients with acute promyelocytic leukaemia, the independent association between INR/PT/APTT levels and bleeding events is uncertain.	✓	NA	X	✓✓	✓✓
ES5.4	In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, subtherapeutic peak APTT levels may be associated with an increased risk of mortality.	✓✓	NA	✓	✓✓	✓✓
ES5.5	In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, supratherapeutic peak APTT levels may be associated with an increased risk of moderate-to-severe bleeding.	✓✓	NA	✓	✓✓	✓✓

ACS, acute coronary syndrome; APTT, activated partial thromboplastin time; ES, evidence statement; INR, international normalised ratio; PT, prothrombin time

✓✓✓=A; ✓✓=B; ✓=C; X=D; **NA**, not applicable (see Table 2.1)

The aim of the literature review was to determine to what extent the presence of an elevated, INR/PT or APTT represents a risk in non-procedural settings, and whether the elevated level should trigger a corrective transfusion of FFP.

The review found a number of relevant prospective (Level II) and retrospective (Level III) cohort studies that focused on patients in three clinical settings: liver disease, acute leukaemia and ACS.

In patients with liver disease, all but one of the included prospective cohort studies found that coagulopathy was an independent risk factor for mortality. One study identified the admission prothrombin ratio as an independent predictor of mortality;¹⁴² another found that INR and APTT were only associated with survival in univariate analysis.¹⁴³ The review did not identify any studies in patients with liver disease reporting whether coagulopathy was an independent risk factor for either bleeding events or subsequent RBC transfusion. Although these studies suggest an association between coagulation parameters and mortality, they do not provide evidence to inform the selection of an appropriate trigger at which transfusion should occur.

None of the commonly used tests have proven to be reliable as predictors of bleeding risk in liver disease. Conventional tests (e.g. PT and APTT) correlate poorly with procedure-related bleeding in these patients, as levels of protein C, antithrombin and tissue factor pathway inhibitor are reduced in parallel with

procoagulant factors. Thus, the balance of pro and anticoagulants may be normal, even in the presence of prolongation of PT and APTT.

Only one retrospective cohort study in patients with acute leukaemia reported an association between coagulation parameters and mortality.¹⁴⁴ This study demonstrated that an INR ≥ 1.5 was an independent risk factor for fatal intracranial haemorrhage, but APTT was not. Only one study considered bleeding risk in acute promyelocytic leukaemia (APML) in relation to coagulation indexes.¹⁴⁵ This study found that neither PT nor APTT were independent risks factors for mortality.

3.5.2 Fibrinogen level and use of cryoprecipitate or fibrinogen concentrate

EVIDENCE STATEMENTS – fibrinogen level and cryoprecipitate or fibrinogen concentrate

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES5.6	In patients with liver disease, an independent association between fibrinogen levels and mortality is uncertain.	X	NA	X	✓✓	✓✓
ES5.7	In patients with acute leukaemia, an independent association between fibrinogen levels and mortality is uncertain.	✓	NA	X	✓✓	✓
ES5.8	In patients with acute promyelocytic leukaemia, an independent association between fibrinogen levels and bleeding events is uncertain.	✓	NA	X	✓✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

Acquired hypofibrinogenaemia may arise in various clinical settings. These include severe liver disease, fulminant hepatic failure, disseminated intravascular coagulation (DIC), post-thrombolysis, massive blood loss and transfusion, and after L-asparaginase therapy for acute lymphocytic leukaemia. The specific diagnosis and management of DIC has not been specifically reviewed in the literature search. However, the British Committee for Standards in Haematology *Guidelines for the diagnosis and management of disseminated intravascular coagulation*¹⁴⁶ are a good reference. A specific review of DIC may be considered in subsequent module updates.

Although FFP contains some fibrinogen, transfusion of cryoprecipitate or fibrinogen concentrate is the most efficient means of fibrinogen replacement. These interventions may also be indicated in patients with the relatively rare conditions of inherited afibrinogenaemia or dysfibrinogenaemia.

The literature review excluded patients in perioperative settings and those with massive blood loss or transfusion, as these populations are covered in other modules of the patient blood management guideline.

In patients with liver disease, the review found one prospective cohort study (Level II) that looked at hospitalised patients with cirrhosis and worsening liver failure.¹⁴³ Fibrinogen level was associated with survival, but only in the univariate analysis. However, because of the poor quality of the evidence, the association between fibrinogen levels and mortality remains uncertain. No studies were found that reported whether fibrinogen level is an independent risk factor for bleeding or for the risk of RBC transfusion in this patient group.

Two relevant retrospective cohort studies (Level III) in patients with acute leukaemia were found. One poor-quality study looked at patients receiving induction chemotherapy for acute promyelocytic leukaemia.¹⁴⁵ Fibrinogen level was not an independent risk factor for bleeding in this setting. The other study examined the risk of fatal intracranial haemorrhage in acute leukaemia patients, but found no significant association between fibrinogen level and fatal intracranial haemorrhage.¹⁴⁴ No studies of acute leukaemia patients were found that reported on an association between fibrinogen level and risk of transfusion.

3.5.3 Platelet count and prophylactic platelet transfusion in patients undergoing chemotherapy and haematopoietic stem cell transplantation

EVIDENCE STATEMENTS – chemotherapy and haematopoietic stem cell transplantation		Evidence	Consistency	Clinical Impact	Generalisability	Applicability
ES5.9	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to the effect on mortality – the difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors versus a higher trigger is uncertain. The effect at lower values is unknown.	✓✓	✓✓	X	✓✓	✓✓
ES5.10	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to major bleeding events – there is no difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors and a higher trigger. The effect at lower values is unknown.	✓✓	✓✓✓	X	✓✓	✓✓
ES5.11	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to RBC transfusion – there is no difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors and a higher trigger. The effect at lower values is unknown.	✓✓	✓✓✓	X	✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; X=D; (see Table 2.1)

RECOMMENDATION – chemotherapy and haematopoietic stem cell transplantation

R8

GRADE B

In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9/L$ in the absence of risk factors, and at $<20 \times 10^9/L$ in the presence of risk factors (e.g. fever, minor bleeding).

PRACTICE POINT – chemotherapy and haematopoietic stem cell transplantation

PP22

In patients undergoing chemotherapy and haematopoietic stem cell transplantation, there is no evidence to support:

- a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding)
- a strategy of therapeutic-only platelet transfusions (i.e. for treatment of clinically significant bleeding).

Further research to determine the safety and efficacy of a lower platelet transfusion trigger is underway.

PP, practice point; R, recommendation

The use of prophylactic platelet transfusions in patients receiving myelosuppressive chemotherapy or undergoing allogeneic haematopoietic stem cell transplantation (HSCT) is significant. It currently accounts for most of the platelet concentrate usage in Australia. In this clinical setting – in the absence of acute bleeding or the need for an invasive procedure – prophylactic platelet transfusion is usually guided by platelet counts.

The review examined studies concerning platelet count and bleeding risk, together with the intervention of platelet transfusion, but excluded studies in perioperative or acute bleeding settings.

The review identified four RCTs (Level II) comparing different platelet transfusion triggers. Three studies¹⁴⁷⁻¹⁴⁹ compared a platelet transfusion trigger of $10 \times 10^9/L$ with one of $20 \times 10^9/L$. Another study used $30 \times 10^9/L$ as the higher trigger.¹⁵⁰ Of these studies, three^{147,149,150} did not demonstrate a significant difference in mortality between the two study arms. These three studies reported bleeding events, but none observed a significant difference in bleeding rates between the two study arms, nor in bleeding rates in relation to a more restrictive platelet transfusion trigger. RBC transfusion rates were reported in all four studies. None of the studies demonstrated significant differences in number of RBC units transfused, or in the number of transfusions, between study arms.

Based on these results, in patients undergoing myelosuppressive chemotherapy or HSCT, the recommended strategy for prophylactic platelet transfusion is at a platelet count of $<10 \times 10^9/L$ in the absence of risk factors, and at $<20 \times 10^9/L$ in the presence of risk factors (see recommendation R8 above).

There is no evidence at this time to support a lower threshold for prophylaxis, or for the absence of prophylaxis. However, these questions are the current focus of two major international RCTs.

3.6 Red blood cell transfusion in chronically transfused patients

Question 6 (Interventional)

In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes?

Hb, haemoglobin

Patients requiring chronic RBC transfusions account for a significant proportion of blood usage. This includes patients with β thalassaemia major, sickle cell disease and myelodysplasia. Hence, appropriate use of red blood cells in these patients is of great importance, both for patient welfare and for the appropriate use of a scarce and valuable resource.

Chronic hypoproduction of RBCs means that regular transfusions are generally required to maintain the Hb at a particular level. The 2001 *Clinical Practice Guidelines on the Use of Blood Components*¹ indicated that maintaining Hb at >80 g/L was likely to be appropriate on the basis of physiological principles. These patients are usually managed as outpatients. Hence, for practical reasons, they are often prescribed a predetermined number of RBC units (intended to achieve a defined Hb concentration), rather than having their response assessed after each unit. In addition, these patients may be deliberately transfused to a higher level of Hb than is physiologically necessary, in an attempt to maximise the interval between transfusions. This decision making appears to be based on historical practice; the triggers for initiating transfusion in such patients are different to the triggers for patients with anaemia who do not have bone marrow dysfunction.

Due to the chronic nature of the disorder, patients with chronic anaemia may receive multiple transfusions over a long period. Therefore, in addition to the usual risks associated with transfusion, patients are at risk of complications such as human leukocyte antigen (HLA) and red cell alloimmunisation, and iron overload. For the latter, use of chelation therapy should be considered.

3.6.1 Thalassaemia

EVIDENCE STATEMENTS – thalassaemia		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES6.1	In patients with thalassaemia, the effect of the pretransfusion Hb threshold on mortality is uncertain.	X	NA	✓	✓✓✓	X
ES6.2	In patients with thalassaemia, a pretransfusion Hb concentration of 90 – 100 g/L may reduce transfusion volume, compared with 100 – 120 g/L.	✓	✓	✓	✓✓	✓✓

ES, evidence statement; Hb, haemoglobin

✓✓✓=A; ✓✓=B; ✓=C; X=D; NA, not applicable (see Table 2.1)

PRACTICE POINT – thalassaemia

PP23

In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.

Hb, haemoglobin; PP, practice point

The use of chronic RBC transfusions intensified in 1978, when iron chelation therapy using subcutaneous desferrioxamine infusions was introduced to improve the management of iron overload in β thalassaemia major. The aim of the transfusions was to prevent severe anaemia and early mortality and to promote growth, development, well-being and quality of life. They were also intended to minimise or prevent the expansion of the marrow mass that leads to bone deformities such as maxillary hyperplasia and extra medullary haematopoietic tissue, which typically occur in liver and spleen and along the vertebral column.

The appearance of any of these complications in infancy and childhood is used as a trigger to commence blood transfusion treatment, with the widely accepted aim of maintaining a pretransfusion Hb concentration of at least 90 – 110 g/L, and a mean of approximately 120 g/L. This pretransfusion Hb concentration was adopted empirically, after trials of lower levels found that some of the complications from under-transfusion (e.g. bone marrow expansion) continued to appear. Hence, in the late 1970s and 1980s, there was widespread adoption of the pretransfusion Hb range of 90 – 110 g/L, which was the maximum achievable with 3 – 4 weekly transfusions. To this day, this treatment is accepted as optimal when combined with adequate chelation therapy. Hypersplenism requiring splenectomy occurs in at least 50% of patients and is usually carried out when the blood transfusion requirement exceeds 200 – 250 ml/kg/year. Splenectomy usually results in a significant reduction in transfusion requirement.

In contrast to β thalassaemia major, recent studies have reported that complications in patients with β thalassaemia intermedia appear to be less common. This is particularly so later in life in patients undergoing regular transfusion, and is more common in patients who have undergone splenectomy. Thus, regular transfusion may become a more common option for management and prevention of complications that occur later in life in this subgroup of patients. However, the management of β thalassaemia intermedia will continue to be personalised until more is known about these late complications.

The adequacy of blood transfusion and chelation therapy in individual treatment centres depends on the adequacy of local resources (including blood banking) and funding for an appropriate iron chelating agent. There are few studies to support this management strategy; however, patients managed in this way are now surviving into the sixth decade of life. The literature review found only a few studies that objectively addressed aspects of these management issues.

One retrospective cohort study of fair quality (Level III) provided support for the association of current pretransfusion level with longer survival.¹⁵¹ The study reported that subjects with a pretransfusion Hb concentration >90 g/L had significantly longer mean survival than those with a level $\leq$ 90 g/L.

Two prospective cohort studies (Level II)^{152,153} and one retrospective cohort study (Level III)¹⁵⁴ investigated the relationship between pretransfusion Hb concentrations and transfusion volume. Cazzola¹⁵⁴ and Masera¹⁵² found that patients maintained with a mean pretransfusion Hb concentration of 90 – 100 g/L and 102 g/L, respectively, required significantly lower transfusion volumes than patients with higher pretransfusion levels. Masera¹⁵² found that this difference was maintained for the first 5 months, after which time there was no significant difference. Cazzola¹⁵⁴ found no differences between subgroups with or without splenectomy, and Masera¹⁵² included only splenectomised patients. Torcharus¹⁵³ reported that paediatric patients with a pretransfusion Hb concentration of >80 g/L had a higher mean transfusion volume than subjects with a mean pretransfusion Hb of 60 – 70 g/L. These results support current practice.

Quality-of-life issues have been important in the optimal management of patients with transfusion-dependent β thalassaemia major. High-quality prospective or retrospective cohort studies are required in this area.

3.6.2 Myelodysplasia

EVIDENCE STATEMENTS – myelodysplasia		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES6.3	In patients with myelodysplasia, no studies were found reporting the effect of the pretransfusion Hb threshold on mortality, transfusion incidence, transfusion volume, thromboembolic events and functional or performance status	NA	NA	NA	NA	NA

ES, evidence statement; NA, not applicable (see Table 2.1)

PRACTICE POINT – myelodysplasia	
PP24	In patients with myelodysplasia who are regularly and chronically transfused, there is no evidence to guide particular Hb thresholds. Decisions around appropriate triggers and frequency of transfusion need to be individualised, taking into account anaemia-related symptoms, functional or performance status, and the patient’s response to previous transfusions.

Hb, haemoglobin; PP, practice point

MDS refers to a group of bone marrow stem cell disorders that involve ineffective production (dysplasia) of the myeloid series. Patients with MDS develop one or more cytopenias due to progressive marrow failure. Although MDS may progress to acute leukaemia, a significant proportion of morbidity and mortality relate to the cytopenias. MDS predominantly occurs in older patients.

Anaemia is common in MDS, and supportive treatment with RBC transfusion has traditionally been prescribed. The main aim of RBC transfusion is to prevent or treat complications such as cardiovascular and cerebrovascular compromise. It is also used to improve the quality of life in MDS patients who have significant symptoms of malaise and fatigue. However, these symptoms may or may not be related to the anaemia, and assessment of the clinical response to the transfusion is therefore important.

The systematic review aimed to identify studies in patients with MDS, to determine at what Hb threshold transfusion should be given to avoid adverse complications. These include morbidity, mortality, and reduced functional or performance status. No studies were identified that assessed an association between pretransfusion Hb concentrations and mortality, functional or performance status, arterial thromboembolic events or RBC transfusion incidence or volume. Eighteen cohort studies were identified that assessed Hb and outcomes in MDS patients. However, none provided analysis related to pretransfusion Hb concentration; rather, they mainly aimed to assess the impact of Hb concentration at diagnosis. Most of the studies found that Hb concentration at diagnosis was a significant predictor of survival; a fact that is well recognised. Only one study reported that Hb concentration may also show a correlation with the results of functional or performance status testing in MDS patients.¹⁵⁵

Thus, there is no evidence to guide clinicians on the Hb threshold for transfusion in patients with MDS and chronic anaemia. Further studies are needed to assess the benefit of transfusion in this population. Details on the use of ESAs in this patient group can be found in Section 3.3.6. Decisions about the need for and the frequency of transfusion require a risk–benefit assessment in each patient, taking into account their functional or performance status and Hb concentration.

ARCHIVED

ARCHIVED

4 Background questions

ARCHIVED

4.1 Interventions to raise haemoglobin levels in patients with malignancies

Background question 1

In patients with malignancies (solid tumours) undergoing radiotherapy, do interventions (transfusion or ESAs) aimed at raising the Hb concentration during radiotherapy affect patient outcomes (e.g. response rate, tumour recurrence or tumour-free survival)?

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin

4.1.1 Tumour hypoxia: pathophysiology and effects

Heterogeneously distributed hypoxic areas ($pO_2 < 2.5$ mm Hg) are seen in up to 60% of locally advanced solid tumours, such as breast, uterine, cervix, head, neck and rectal cancers, soft tissue sarcomas and malignant melanomas.¹⁵⁶ A high incidence of hypoxic areas has been correlated with aggressive tumour behaviour and a propensity for metastasis.

Hypoxia affects signalling pathways involved in angiogenesis, glucose transport, pH regulation and erythropoiesis.¹⁵⁷ Hence, tumours become hypoxic because of the development of abnormal vasculature. The hypoxia-inducible factor (HIF) family of transcription factors is important in the cellular response to oxygen homeostasis; overexpression of HIF-1 in human cancers correlates with poor prognosis and increased tumour aggression.¹⁵⁸ Sustained tumour hypoxia alters the response to radiation and to many chemotherapeutic agents in cell lines, but this effect also depends on microenvironmental pH and glucose depletion.

Anaemia is common in patients with solid tumours, and is related to the tumour's malignancy and treatment. An association between low haemoglobin levels and poor outcome of both radiotherapy and chemotherapy has been observed in various solid tumours.^{159,160} Reduced blood oxygen carrying capacity in anaemia may be a major contributor to tissue hypoxia, because the abnormal tumour vasculature is less able to compensate for anaemia by increasing tissue perfusion.

4.1.2 Tumour hypoxia and radiotherapy resistance

High-energy photons used in radiotherapy induce deoxyribonucleic acid (DNA) damage. The photons can either directly cause electrons to ionize DNA helix atoms, or can produce highly reactive free radical species, which then interact with and damage DNA. Unrepaired DNA damage inhibits cell proliferation and leads to cell death. The presence of oxygen contributes to the indirect process by prolonging the life span of the free radicals. Oxygen also decreases the ability of cells to repair DNA damage, so that well-oxygenated cells are more radiosensitive than hypoxic cells.

Hypoxia may also contribute to tumour radiation resistance. This can be caused by altered cell proliferation kinetics, reduction of apoptosis and differentiation, and reduced cell growth associated with slowed protein synthesis. Hypoxia may also increase malignant progression and aggressiveness through clonal selection and genome changes, with an adverse effect on patient outcomes.

4.1.3 Impact of correction of anaemia on radiotherapy outcome

Anaemia (using Hb thresholds of 90–145 g/L) has been associated with a reduced response to therapy and shortened survival in cervical, bladder, bronchial, and head and neck cancers.¹⁶¹

Erythropoiesis-stimulating agents

ESAs reduce therapy-related anaemia and need for transfusion.^{95,162} However, locoregional progression-free survival was significantly worse in the treatment arm in a large multi-institutional placebo-controlled phase III trial of ESA therapy in patients undergoing radiotherapy for head and neck cancer.¹⁶³

A Cochrane review¹⁶⁴ examined the use of ESAs with radiotherapy or chemotherapy in head and neck cancer patients and demonstrated poorer survival in patients receiving ESAs, although the target Hb was higher than currently regarded as appropriate in four of the five included trials.

The Gynecologic Oncology Group (GOG) trial 0191 assessed the effect of using ESAs to maintain the Hb at 100 g/L compared with ESA treatment or transfusion to a Hb of 120–130 g/L in women with locally advanced cervical cancer.¹⁶⁵ The study was closed early due to increased thromboembolic events in the latter arm. The three-year progression-free survival and overall survival were inferior in the ESA treatment group.

The adverse outcomes may result from an excess of thromboembolic events among patients treated with a high Hb target. ESAs may also promote tumour progression, because erythropoietin receptors may be expressed on the surface of some tumour cell lines.

ESAs are not currently approved by the Therapeutic Goods Administration (TGA) for use in Australia for treatment of anaemia due to malignancy or chemotherapy.

Red blood cell transfusion

The view that transfusing RBCs to maintain a Hb of 125 g/L in patients undergoing radiotherapy for solid tumours is associated with a reduced local relapse rate is based on a 1978 publication.¹⁶⁶ However, subsequent analysis of the study, based on intention to treat, demonstrated that there was no difference in disease-related mortality. A recent study evaluating the prognostic significance of anaemia and its modification by transfusion in head and neck cancer patients treated with radiotherapy showed no benefit.¹⁶⁷ Transfusion may improve oxygen delivery in profoundly anaemic patients, but does not necessarily overcome other factors leading to tumour hypoxia.

It has been proposed that increased morbidity and mortality in transfused patients is due to immunosuppression.^{168–170} The review by Varlotto and Stevenson¹⁷¹ concluded that correction of anaemia by blood transfusions has had an adverse effect on patient survival. The authors postulated that this was due to modulation of inflammatory or immunosuppressive pathways.

The relationship between anaemia, tumour hypoxia and the effects of treatment to correct anaemia in patients with solid tumours is far more complex than initially perceived. Hypoxia is most likely predominantly related to abnormal tumour vasculature, and correction of anaemia has not been demonstrated to improve the outcome of radiotherapy. The use of ESAs, particularly with higher Hb targets, has been associated with an adverse impact on survival in patients with malignancy.

Transfusion decisions for patients undergoing radiotherapy are thus based on the principles used for other patients with cancer (see Section 3.2.4).

4.2 Assessment of patients after red blood cell transfusion

Background question 2

When should a patient be retested after a transfusion to assess the response, guide whether further transfusions are required and avoid over transfusion?

When prescribing a RBC transfusion, deciding how many units to transfuse is as important as the transfusion decision itself, because each unit transfused carries additional risks (see Appendix B).

There is a growing body of literature covering appropriate Hb thresholds or triggers for RBC transfusion, both in the general population and in various clinical subgroups. However, these studies generally do not address the issue of over-transfusion and its attendant risks, which are of significant practical importance.^{172,173}

When considering the decision to transfuse and the dosage, it is best to undertake careful clinical assessment of patients. A single-unit transfusion practice approach should be undertaken, with further clinical assessment after transfusion. Further transfusions are *not* required if the signs and symptoms are relieved. Clinical experience suggests that, in many patients, it may take 24 hours or more for patients to report an improvement in symptoms.

In some situations, prescribing more than one unit at a time may be appropriate; for example, where there is significant ongoing or anticipated blood loss, severe anaemia or the patient has chronic transfusion requirements (e.g. for bone marrow failure). The number of units prescribed, however, should still be carefully considered based on individual patient factors.

There is limited information in the literature about when to test the Hb level after a RBC transfusion. Where indicated, transfusion of a single unit of RBC followed by clinical reassessment is appropriate. This assessment will guide the decision on whether to retest the Hb level. One study reported a high correlation between Hb levels taken at 15 minutes, 1 hour and 2 hours after transfusion.¹⁷⁴

ARCHIVED

ARCHIVED

5 Future directions

The systematic review for this module found adequate evidence to confirm that anaemia is an independent predictor of poorer patient outcomes. However, the findings did not prove that anaemia causes these outcomes, or that correction of the anaemia will reverse the outcomes. Since aetiological questions cannot give rise to recommendations, further investment in systematic reviews in this area is unwarranted.

There was surprisingly little evidence for the benefit of RBC transfusions to correct anaemia in both general and specific medical populations. Thus, it has been difficult to provide guidance on RBC transfusion thresholds while ensuring a patient focus. Any future studies should focus on a formal evaluation of effects on well-being, because this is one of the most common justifications for transfusion. In addition, although there is some evidence of short-term harm associated with transfusion, there is uncertainty about the long-term consequences.

5.1 Evidence gaps and areas of future research

In this review, there were a number of areas where evidence was not sufficient to generate recommendations. Further research in the following areas may be profitable:

- evaluating the incidence, prevalence and management of anaemia (including identification and treatment of underlying causes) in Aboriginal and Torres Strait Islander populations
- identifying the clinical factors, including Hb concentration, that should guide RBC transfusion in medical patients
- evaluating the role and timing of RBC transfusion in patients with acute upper gastrointestinal blood loss, focusing on the effect on rebleeding
- investigating the management of bleeding patients administered fibrinolytics, and newer anticoagulant and antiplatelet agents
- identifying subsets of patients with cancer in whom ESAs can safely be used
- identifying medical populations who may benefit from the use of FFP
- evaluating the use of fibrinogen concentrate as an alternative to cryoprecipitate
- determining the appropriate trigger for RBC transfusion in patients with thalassaemia and patients with bone marrow failure
- validating the signs and symptoms that indicate a need for RBC transfusion, and evaluating changes in post-transfusion clinical and laboratory indexes over time, to guide management.

5.2 Topics for future consideration

The following topics were not included in the systematic review, but may be considered in revisions of this module:

- the effect of the age of blood on patient outcomes
- the appropriate use of blood products in patients with DIC.

ARCHIVED

ARCHIVED

6 Implementing, evaluating and maintaining the guidelines

The NBA, in collaboration with the Steering Committee and EWG members, developed a plan to guide appropriate communication on the implementation of this module. The plan identifies target audiences for the module, strategies and tools for effective implementation, communication channels and key messages.

Continued re-evaluation of the guidelines is necessary to reduce variation in practice patterns, support appropriate use of blood component therapy, and reduce inappropriate exposure of patients to blood components.¹⁷⁵ A plan was designed to evaluate implementation of the six modules of the guidelines, and to determine:

- the extent to which the guidelines influence changes in clinical practice and health outcomes
- what factors (if any) contribute to noncompliance with the guidelines.

The results of the evaluation will be used to inform future review of the guidelines. Economic issues were considered when formulating the evidence-based recommendations. The recommendations are likely to reduce product associated expenditure. All recommendations (R1–R8) within this Module either constrain the use of more expensive products (such as blood and blood products and erythropoietin stimulating agents) or replace them with less expensive products (such as iron therapy).

Patient blood management however, requires effective coordination of care. The cost of introducing a coordinated patient blood management approach is anticipated to be offset by savings in reduced product consumption. The NBA, together with the Jurisdictional Blood Committee (JBC) and key stakeholders, is developing a program to facilitate uptake of the PBM guidelines.

The program will include the development of a comprehensive toolkit to support the introduction of patient blood management practices in the clinical setting. The toolkit is being developed with the help of a network of patient blood management practitioners, who will facilitate uptake of the guidelines. The NBA has also funded the development of an online iron deficiency anaemia course within the BloodSafe eLearning Program. Funding has been provided for this course to be marketed to health-care practitioners in the primary and secondary care setting. In addition, the NBA is working with the Australian Commission on Safety and Quality in Healthcare (ACSQHC) to develop a hospital guide to support the implementation of the *National Safety and Quality Health Service Standards*.¹⁷⁶ The guide will provide links to the patient blood management guidelines and toolkit, and the BloodSafe eLearning course. These resources provide explicit tools to support uptake of the recommendations in this module.

This module will be reviewed and amended in 2017, unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need for an earlier review.

The PBM Guidelines Project Manager at the NBA will convene the group of experts to undertake the review, and will be the person to contact about major issues, events or practice changes.

To provide feedback and inform future reviews of this module, please send any comments on its content or implementation, or on the accompanying materials, to:

- Email: guidelines@blood.gov.au
- Mail: Patient Blood Management Guidelines
National Blood Authority
Locked Bag 8430
Canberra ACT 2601
- Fax: (02) 6151 5300

Any correspondence will be forwarded to the PBM Guidelines Project Manager for consideration in the next scheduled review.

A list of colleges and societies that have endorsed this module of the guidelines will be available on the NBA website.^c

^c <http://www.blood.gov.au/>

ARCHIVED

ARCHIVED

Appendix A

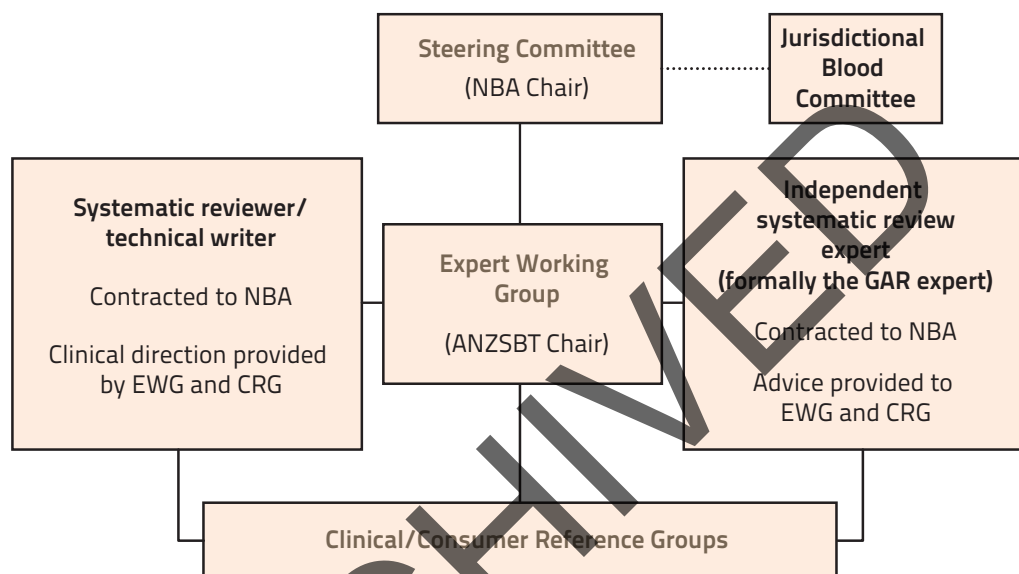
Governance

ARCHIVED

A1 Management framework for guideline development

Figure A1 illustrates the framework used to manage the development of the six modules of the guidelines, described in Section 1.2 of Chapter 1.

Figure A1 Management framework for development of the guidelines



ANZSBT, Australian & New Zealand Society of Blood Transfusion; CRG, Clinical/Consumer Reference Group; EWG, Expert Working Group; GAR, NHMRC Guidelines Assessment Register; NBA, National Blood Authority

A2 Terms of reference

Steering Committee

The overarching Steering Committee was established to provide coordination and direction for development of the guidelines. It was chaired by the NBA, with representation from the ANZSBT the Jurisdictional Blood Committee and a clinical representative from the Australian Government Department of Health and Ageing. The role of the Steering Committee was to:

- develop and oversee the project plan for the revision of the guidelines
- recommend the membership of the EWG to the NBA Chief Executive Officer, who will appoint the recommended members
- endorse the scope of the project as proposed by the EWG, and the process by which it will be undertaken
- ensure that there is effective communication and consultation with all relevant stakeholders for the duration of the project, including the development of a communications and engagement strategy that meets NHMRC requirements

- provide information on the project through the NBA to the JBC
- review resources that are dedicated to the project, to ensure that they are sufficient for the project to meet its deadlines
- review and approve revisions to the project plan and terms of reference
- address other matters as raised by members of the Steering Committee or EWG.

Expert Working Group

The EWG was formed to advise the Steering Committee about the scope and structure of the guidelines, and to determine the focus of the systematic review of the evidence-based literature. The group's terms of reference were to:

- consider the scope of the project and proposed structure of the guidelines as referred by the Steering Committee, and, if necessary, to present recommendations for revisions to the Steering Committee
- under the guidance of the NHMRC independent systematic review expert, formulate the clinical questions to be answered by the literature review
- provide clinical oversight for the development of the content of the guidelines, in particular, ensuring that:
 - the research undertaken is comprehensive
 - the quality of the revised guidelines will meet with clinical approval
- provide recommendations on the terms of reference for the CRGs and oversee coordination of the activities of the CRGs
- ensure appropriate engagement by consumers at all relevant points
- assist in the development or review of tools and strategies to support the implementation and audit of the guidelines and review their uptake
- facilitate consultation and uptake of the guidelines
- respond to any additional requirements to ensure compliance with the NHMRC guidelines development processes.

Systematic reviewers and technical writers

The NBA contracted systematic reviewers and technical writers to conduct systematic reviews of the scientific literature and provide technical writing services to produce each module and technical reports.

Clinical/Consumer Reference Groups

A CRG was formed to review each phase of the guidelines during development. With the assistance of technical writers, the CRGs formulated recommendations aimed at optimising patient blood management based on systematic review findings, or, in the absence of evidence, developed practice points through a consensus-based process. The CRGs also provided advice to the EWG on guideline relevance and utility for targeted service providers and recipients who will use or benefit from the guidelines. Pertinent terms of reference for guidelines development included the following:

- the CRGs may review and offer advice on the set of questions to be put to the systematic review for the project
- the CRGs may review the draft guidelines and consumer materials, and offer advice on the way information is presented in terms of relevance and utility to the groups they represent
- the CRGs will not have authority or decision-making power over how that advice is used.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

Ms Stephanie Gunn (Chair)	National Blood Authority
Mr Ken Davis	Australian & New Zealand Society of Blood Transfusion
Prof Henry Ekert	Australian Government Department of Health and Ageing
Ms Sue Ireland	Jurisdictional Blood Committee
Dr Amanda Thomson	Australian & New Zealand Society of Blood Transfusion

Expert Working Group

Dr Craig French (Co-chair)	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society
Dr Amanda Thomson (Co-chair)	Australian & New Zealand Society of Blood Transfusion
A/Prof Donald Bowden	Thalassaemia Australia
A/Prof Mark Dean	Haematology Society of Australia and New Zealand & Royal Australasian College of Physicians
Mr Shannon Farmer	Patient Blood Management Advocate
Dr Chris Hogan	National Blood Authority
Ms Janine Learmont	Royal College of Nursing, Australia
Dr Helen Liley	Royal Australasian College of Physicians, Paediatric & Child Health Division
Dr Robert Lindeman	Royal College of Pathologists of Australasia
A/Prof Larry McNicol	Australian & New Zealand College of Anaesthetists
Prof Michael Permezel	Royal Australian & New Zealand College of Obstetricians and Gynaecologists
Dr Kathryn Robinson	Australian Red Cross Blood Service
Dr Richard Seigne	Australian & New Zealand Society of Blood Transfusion
Dr Philip Truskett	Royal Australasian College of Surgeons
Dr John Vinen	Australasian College for Emergency Medicine

Clinical/Consumer Reference Group – Medical Module

A/Prof Mark Dean (Chair)	Haematologist	Royal College of Physicians & Haematology Society of Australia & New Zealand
Dr Lilon Bandler	General practitioner and Indigenous health representative	Royal Australian College of General Practitioners
A/Prof Donald Bowden	Haematologist	Thalassemia Australia
Prof John Duggan*	Gastroenterologist	Independent expert – gastroenterology
Mr Shannon Farmer	Researcher	Patient Blood Management Advocate
Dr Craig French	Intensive care physician	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society
Dr Chris Hogan	Haematologist	National Blood Authority
Dr Robert Lindeman	Haematologist	Royal College of Pathologists Australia
Prof Lawrence McMahon*	Nephrologist	Independent expert – renal medicine
Ms Penny O'Beid	Clinical Nurse Consultant, Transfusion Medicine	Royal College of Nursing Australia
Dr Kathryn Robinson	Haematologist	Australian Red Cross Blood Service
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion

* Two members joined the CRG for the final four of 12 meetings after the review of the evidence and formulation of recommendations. This additional membership was sought to provide specialist input for specific populations (i.e. renal medicine and gastroenterology) and to ensure that the guidance developed by the CRG accorded, in so far as the evidence allowed, with other guidelines for these specific populations

Background research

Dr Nina Dhondy	Haematology Registrar	Royal North Shore Hospital, Sydney
Dr Chris Hogan	Haematologist	National Blood Authority
Dr Robert Lindeman	Haematologist	Royal College of Pathologists Australia
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion

Acknowledgements – additional clinical input

A/Prof Jane Andrews	Gastroenterologist	Royal Adelaide Hospital
Dr Jeffrey Roland	Geriatrician	The Prince Charles Hospital
Dr Jenny Shannon	Oncologist	Nepean Cancer Care Centre

Independent systematic review expert

Ms Tracy Merlin	Adelaide Health Technology Assessment (AHTA), University of Adelaide
-----------------	---

Project Management and Committee Secretariat – provided by the NBA

Ms Leia Earnshaw	A/g Assistant Director, Blood Sector Clinical Development
Dr Paul Hyland	Assistant Director, Blood Sector Clinical Development
Ms Jennifer Roberts	Director, Blood Sector Clinical Development

Systematic review team

Ms Nimita Arora	OptumInsight (Senior Project Leader)
Dr Kristina Coleman	OptumInsight (Principal Analyst)
Dr Briony Jack	OptumInsight (Research Analyst)
Mr Gregory Merlo	OptumInsight (Senior Analyst)

Medical writing and technical editing – OptumInsight

Dr Hilary Cadman	Cadman Editing Services (independent contractor to OptumInsight)
------------------	--

A4 Conflict of interest

All members of the Steering Committee, CRG, EWG and systematic review team declared any interests before starting work on the guidelines. Interests were also reviewed at intervals, and were required to be declared at the start of each meeting. The NBA keeps a register of all declared interests. If an interest is declared, the CRG decide by consensus if it affects the proceedings. If the interest is considered to be competing or in conflict, the Chair can prevent the member from participating in discussions and decisions pertaining to the declared interest. Three members declared interests during the guideline development process. Mr Shannon Farmer declared the following patient advocacy roles: the Society for the Advancement of Blood Management, the Medical Society for Blood Management and the Network for Advancement of Transfusion Alternatives. Professor Lawrence McMahon declared that he was a prescriber of erythropoiesis stimulating agents. He declared travel grants to attend the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Annual Scientific Meeting in 2010 from Roche and in 2012 from Amgen. He received a research grant from Amgen in 2009 and an unrestricted educational grant for research from Roche in 2011. He was on the Roche Advisory Board for Mircera (continuous erythropoietin receptor activator) in 2008. Dr Kathryn Robinson declared an interstate airfare and accommodation for one night paid directly by Aspen Pharmacare for presenting at an educational iron forum organised by Aspen in February 2008; information from her presentation was used for an Aspen educational newsletter but no payment was received.

The chair considered these declarations and determined that they did not constitute a sufficient conflict to require members to leave the room or excuse themselves from discussion at any time during the guideline development process. No other members declared any interests.

ARCHIVED

Appendix B

Transfusion risks in the context of patient blood management

Traditionally, it has been assumed that blood transfusion benefits patients; however, a benefit has not been demonstrable in many clinical scenarios. In addition, evidence is accumulating that serious non-viral adverse events, such as transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI), are more common than previously thought, and that more recently identified conditions (e.g. transfusion-related immunomodulation) may cause patients harm.

The risk of transmission of infectious diseases through blood transfusions has reduced significantly in recent years, through improved manufacturing and laboratory processes. However, there is potential for transfusion of an unrecognised infectious agent.

Despite improvements in systems management, there remains a risk of transfusion-related harm due to administrative error. Such an error has the potential to result in acute haemolytic reaction from ABO incompatibility, which may be fatal.

If the patient requires therapy for anaemia, thrombocytopaenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, and should:

- take into account the full range of available therapies
- balance the evidence for efficacy and improved clinical outcome against the risks
- take into account patient values and choices.

In the process of obtaining informed consent, a clinician should allow the patient sufficient time to ask questions, and should answer those questions. If the patient is unable to speak or understand English, the clinician may need to involve an interpreter. In certain contexts, a trained medical interpreter may be required (rather than a family member or a friend). Written information and diagrams may be appropriate in certain circumstances to aid understanding.

All elements of the consent process should reflect local state, territory or national requirements.

Table B.1 summarises transfusion risks, and Table B.2 presents the Calman Chart, which may be useful to clinicians for explaining risks to patients.¹⁷⁷

Table B.1 Transfusion risks

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Transfusion-related acute lung injury	1 in 1200 – 190,000	Low to minimal
Haemolytic reactions	Delayed: 1 in 2500 – 11,000 Acute: 1 in 76,000 Fatal: Less than 1 in 1 million	Low to very low Very low Negligible
Anaphylactoid reactions or anaphylaxis (usually due to IgA deficiency)	1 in 20,000 – 50,000	Very low
Bacterial sepsis: platelets	1 in 75,000	Very low
Bacterial sepsis: red blood cells	1 in 500,000	Minimal
Hepatitis B	Less than 1 in 1 million	Negligible
Hepatitis C	Less than 1 in 1 million	Negligible
Human immunodeficiency virus	Less than 1 in 1 million	Negligible
Human T-lymphotropic virus (types 1 and 2)	Less than 1 in 1 million	Negligible

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Malaria	Less than 1 in 1 million	Negligible
Variant Creutzfeldt-Jakob disease (not tested)	Never reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

^a Risk per unit transfused unless otherwise specified

^b See Calman 1996¹⁷⁷

Source: Australian Red Cross Blood Service website (www.transfusion.com.au)

Note: The above estimates may change over time. Refer to the Australian Red Cross Blood Service website (www.transfusion.com.au) for the most recent risk estimates.

Table B.2 Calman Chart^a (United Kingdom risk per one year)

RATING	RATE	EXAMPLE
Negligible	<1 in 1,000,000	Death from lightning strike
Minimal	1 in 100,000 – 1,000,000	Death from train accident
Very low	1 in 10,000 – 100,000	Death from an accident at work
Low	1 in 1,000 – 10,000	Death from a road accident
High	>1 in 1,000	Transmission of chicken pox to susceptible household contacts

^a See Calman 1996¹⁷⁷

ARCHIVED

Appendix C

Blood sectors

ARCHIVED

C1 Australian blood sector

Standing Committee on Health and Australian Health Ministers' Advisory Council

The Standing Committee on Health (SCoH) is responsible for the oversight and management of the Australian blood sector. The committee's responsibilities include national policy and financial decisions in relation to the supply of blood and blood products, and the determination of which products and services can be bought with public funds. SCoH oversees the implementation of the National Blood Agreement (described below), and is supported in its roles by the Australian Health Ministers' Advisory Council (AHMAC).

Clinical, Technical and Ethical Principal Committee

The Clinical, Technical and Ethical Principal Committee (CTEPC) was established in 2006 to consider and provide advice to the AHMAC on a range of issues. Areas covered include:

- clinical, technical and medico-ethical developments that are likely to affect more than one jurisdiction
- options for ongoing coordination of the clinical and technical services that are managed on a national basis
- the appropriateness, effectiveness and safety of clinical and technical developments
- any policy implications arising from the issues considered by the committee
- the impact of clinical and technical developments on the delivery and management of health care and other services
- the impact of clinical and technical developments outside the health-care sector.

Jurisdictional Blood Committee

All Australian governments are represented on the JBC, which was established by the National Blood Agreement in 2003. The committee:

- is the conduit between governments and the NBA
- represents the Australian state and territory governments' positions on:
 - blood policy, demand, supply planning and product distribution
 - funding
 - evidence-based approaches to emerging products, services and technologies
- oversees the NBA's role in blood supply contracting.

The committee is the primary body responsible for providing advice and support on these matters to the SCoH through the CTEPC (of which it has been a subcommittee since September 2006) and the AHMAC.

National Blood Authority

The NBA was established in 2003 as an Australian Government agency within the health and ageing portfolio. It is responsible for ensuring the adequate, safe, secure and affordable supply of blood and blood products. The role of the NBA is outlined in the *National Blood Authority Act 2003* and the National Blood Agreement.

Part 5 of the National Blood Agreement requires the development and implementation of specific safety and quality strategies, including development, implementation and review of evidence-based national clinical practice guidelines for blood, blood products and blood-related services. The aim is to encourage best practice in the management and use of such products and services.

Therapeutic Goods Administration

The TGA is the regulator for blood and blood products in Australia. The TGA is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Therapeutic Goods Act 1989*
- auditing good manufacturing practice
- issuing product recalls
- modifying safety standards
- issuing directives such as donor deferral.

Australian Red Cross Blood Service

The Australian Red Cross Blood Service was established as a national organisation in 1996. It is responsible for collecting, processing and distributing blood and blood components sourced from voluntary donors in Australia. The Australian Red Cross Blood Service works alongside Australian regulators, government departments, and commercial and professional organisations, and with international bodies, to constantly review and improve the safety and provision of blood and blood components in Australia. The Australian Red Cross Blood Service also has significant transfusion medicine expertise and clinical involvement.

C2 New Zealand blood sector

Ministry of Health

The New Zealand Minister of Health is the government owner of the New Zealand Blood Service (NZBS). The Minister appoints the NZBS Board and approves the Statement of Intent and Output Agreement.

The Ministry of Health monitors the performance of the NZBS, and works closely with the organisation in setting the overall strategic direction for the provision of blood and blood products in New Zealand.

Medsafe

Medsafe is the regulator for blood and blood products in New Zealand. Medsafe is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Medicines Act 1981* and *Medicines Regulations 1984*
- auditing and licensing blood centres in accordance with good manufacturing practice
- issuing product recalls
- approving changes to the NZBS Collection and Manufacturing Standards.

New Zealand Blood Service

The NZBS is a Crown Entity established under the *New Zealand Public Health and Disability Act 2000*. Its legislated purpose and core activity is the safe, timely, high-quality and efficient provision of blood and blood products to clinicians for the people of New Zealand. It also provides related services, including matching of patients and donors before organ or tissue transplantation, and provision of tissue banking (skin, bone and stem cell services).

The NZBS Board is appointed by, and responsible to, the Minister of Health, and performs strategic and governance functions in accordance with the Act.

The NZBS works closely with regulators, the Ministry of Health and international agencies to monitor international developments in the field of transfusion medicine, to develop national policies and to implement them as appropriate in the New Zealand setting.

In addition to its role in collecting, processing and distribution of blood and blood products, the NZBS is actively involved in the provision of blood banking and clinical services within New Zealand's major hospitals.

ARCHIVED

ARCHIVED

ARCHIVED

Appendix D

Process report

ARCHIVED

D1 Development process

A review by the NBA of the 2001 *Clinical Practice Guidelines on the Use of Blood Components*¹ led to a decision by the NHMRC, ANZSBT and NBA to develop a series of six guidelines on patient blood management, of which this document is the third. The guidelines development process was initiated by a Steering Committee chaired by the NBA. In 2008, an EWG was formed to oversee development of the series of guidelines.

A CRG, with membership including a patient blood management advocate and representation from relevant colleges and societies, was established to develop the medical module. The CRG received assistance from systematic reviewers and a technical writer, and advice and mentoring from a systematic review expert. Further details of the governance framework are provided in Section 1.2 and Appendix A.

D2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EWG and the CRG for this guideline, and further refined through consultation among the systematic reviewers, CRG, NBA and the systematic review expert.

D3 Methodology

Methods are outlined in Chapter 2, with greater detail given in the technical reports. Briefly, the clinical research questions for systematic review were structured according to three criteria: PICO ('population, intervention, comparator and outcome') for intervention questions, PPO ('population, predictor and outcome') for prognostic questions, or PRO ('population, risk factor and outcome') for aetiology questions. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG. The primary databases searched were EMBASE, Medline, the Cochrane Library Database and PreMedline. Additional searches were conducted of Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published between 1966 and July 2010.

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated according to NHMRC levels of evidence hierarchy, dimensions of evidence, and quality assessment criteria.^{14,178} An NHMRC evidence statement form was completed for each systematically reviewed research question. Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation.¹⁴ Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was required to supplement recommendations and guide clinical practice, the CRG developed practice points through a consensus-based process.

D4 Public consultation

Public consultation was conducted from 23 January to 16 March 2012, during which time the draft module was available on the NBA website.^d Notification was posted in *The Australian* national newspaper, and the NBA invited a range of stakeholders, committees, working groups and interested people to provide submissions.

Eleven submissions were received. The CRG met in April 2012 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

D5 Finalising the guidelines

The final drafts of the module and technical reports were reviewed by a guidelines development expert (formerly a Guidelines Assessment Register consultant) to assess compliance with NHMRC requirements for externally developed guidelines. The module was then reviewed by an AGREE II expert to assess it against international quality standards. The module and accompanying documents were then sent to the NHMRC for methodological and independent peer review on 20 April 2012.

Approval from the NHMRC was received on 18 July 2012.

ARCHIVED

^d <http://www.blood.gov.au/>

ARCHIVED

Appendix E

Product information

For information on blood products available in Australia, see the website of the Australian Red Cross Blood Service (www.transfusion.com.au).

For information on blood products available in New Zealand, see the website of the New Zealand Blood Service (www.nzblood.co.nz).

ARCHIVED

Appendix F

Summary of recommendations and practice points by clinical condition

F1 General medical

Identifier	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP3	Direct evidence is not available in general medical patients.³ Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ³ Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell

F2 Cardiac – acute coronary syndrome

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
R1 GRADE C	In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.	3.2.2
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1
PP5	In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate.	3.2.2
PP6	In patients with ACS and a Hb concentration of 80 – 100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits.	3.2.2

ACS, acute coronary syndrome; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell

^e As noted above, recommendations are graded and practice points are not.

F3 Heart failure

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
R3 GRADE B	In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. This is consistent with the 2011 update to the <i>Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006</i>.² Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.	3.3.2
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1

^e As noted above, recommendations are graded and practice points are not.

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1
PP7	In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status. For further guidance on how to manage patients with heart failure, refer to general medical or ACS sections, as appropriate (R1, R3, PP3–PP6).	3.2.3

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; NYHA, New York Heart Association; PP, practice point; R, recommendation; RBC, red blood cell

^e As noted above, recommendations are graded and practice points are not.

F4 Cancer

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1
PP8	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.	3.2.4 3.3.1

^e As noted above, recommendations are graded and practice points are not.

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
PP9	There is a lack of specific evidence relating to the effects of RBC transfusion in patients with cancer. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia. When treating patients with cancer, refer also to the general medical population PP1–PP4.	3.2.4
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
R2 GRADE A	In cancer patients with anaemia, the <i>routine</i> use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.	3.3.1
PP12	In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.	3.3.1

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell

F5 Gastrointestinal

Identifier	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1

^e As noted above, recommendations are graded and practice points are not.

Identifier	Guidance – recommendations and practice points	Relevant section of document
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1
PP10	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. Therefore, a more restrictive approach may be appropriate. There are no data to support a specific Hb treatment target in these patients.	3.2.5
PP11	For critically bleeding patients, refer to <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion</i> (2011). ⁴	3.2.5
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
PP15	In patients with IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.	3.3.5

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; IBD, inflammatory bowel disease; IV, intravenous; PP, practice point; RBC, red blood cell

F6 Chronic kidney disease

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
R4 GRADE B	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient. Note: The CARI guidelines recommend a Hb target between 100–115 g/L ⁵	3.3.3
R5 GRADE C	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to relieve fatigue, after consideration of risks and benefits for the individual patient. Note: The CARI guidelines recommend a Hb target between 100–115 g/L ⁵	3.3.3
R6 GRADE B	In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.	3.3.3
R7 GRADE B	In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the routine use of ESAs is not recommended because of the increased risk of cancer-related mortality.	3.3.3
PP13	ESA use is less effective in patients with chronic renal failure who have absolute or functional iron deficiency.	3.3.3
PP14	For comprehensive information about ESA and iron therapy in patients with CKD, refer to CARI iron guidelines. ⁵	3.3.3
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1

^e As noted above, recommendations are graded and practice points are not.

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70 – 100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1

ACS, acute coronary syndrome; CARL, Caring for Australasians with Renal Impairment; CHF, chronic heart failure; CKD, chronic kidney disease; CRG, Clinical/Consumer Reference Group; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; PP, practice point; R, recommendation; RBC, red blood cell

^e As noted above, recommendations are graded and practice points are not.

F7 Chemotherapy and haematopoietic stem cell transplantation

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP3	Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70–100 g/L, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. ▪ Hb concentration >100 g/L, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. ^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	3.2.1
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1

^e As noted above, recommendations are graded and practice points are not.

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
PLATELETS		
R8 GRADE B	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9/L$ in the absence of risk factors, and at $<20 \times 10^9/L$ in the presence of risk factors (e.g. fever, minor bleeding).	3.5.3
PP20	Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.	3.4.3
PP22	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, there is no evidence to support: ▪ a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding) ▪ a strategy of therapeutic-only platelet transfusions (i.e. for treatment of clinically significant bleeding). Further research to determine the safety and efficacy of a lower platelet transfusion trigger is underway.	3.5.3

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; HIT, heparin-induced thrombocytopenia; PP, practice point; R, recommendation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura

^e As noted above, recommendations are graded and practice points are not.

F8 Thalassaemia and myelodysplasia

Identifier	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP23	In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.	3.6.1
PP24	In patients with myelodysplasia who are regularly and chronically transfused, there is no evidence to guide particular Hb thresholds. Decisions around appropriate triggers and frequency of transfusion need to be individualised, taking into account anaemia-related symptoms, functional or performance status, and the patient's response to previous transfusions.	3.6.2
PLATELETS		
PP21	In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.⁹ Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness). Therapeutic platelet transfusions could be considered for treatment of bleeding.	3.4.3

Hb, haemoglobin; PP, practice point

F9 Coagulopathy

Identifier	Guidance – recommendations and practice points	Relevant section of document
FRESH FROZEN PLASMA		
PP16	The <i>routine</i> use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment. The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.	3.4.1
PP17	For guidance on the use of FFP in specific patient groups, refer to: ▪ <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion</i> (2011)⁴ ▪ <i>Patient Blood Management Guidelines: Module 2 – Perioperative</i> (2012)⁶ ▪ <i>Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis</i> (2004)⁷ ▪ AHCDO guidelines for patients with specific factor deficiencies (http://www.ahcdo.org.au) ▪ TTP: <i>Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004).⁸	3.4.1
CRYOPRECIPITATE OR FIBRINOGEN CONCENTRATE		
PP18	The routine use of cryoprecipitate or fibrinogen concentrate in medical patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified; where transfusion is considered necessary, the risks and benefits should be considered for each patient. Specialist opinion is advised for the management of DIC.	3.4.2
PP19	For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to: ▪ <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion</i> (2011)⁴ ▪ AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) ▪ TTP: <i>Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004).⁸	3.4.2

AHCDO, Australian Haemophilia Centre Directors' Organisation; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; PP, practice point

F10 Thrombocytopenia

Identifier	Guidance – recommendations and practice points	Relevant section of document
PLATELETS		
PP20	Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.	3.4.3
PP21	In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.⁹ Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness). Therapeutic platelet transfusions could be considered for treatment of bleeding.	3.4.3

HIT, heparin-induced thrombocytopenia; PP, practice point; TTP, thrombotic thrombocytopenic purpura

ARCHIVED

References

ARCHIVED

- 1 National Health and Medical Research Council (NHMRC) and Australasian Society of Blood Transfusion (ASBT) (2001). *Clinical practice guidelines on the use of blood components*, NHMRC, Canberra, Australia.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp78.pdf
- 2 National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (2011). *Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006 (update)*.
- 3 National Blood Authority (NBA) (In preparation). *Patient blood management guidelines: Module 4 – Critical care*. NBA, Canberra, Australia.
- 4 National Blood Authority (NBA) (2011). *Patient blood management guidelines: Module 1 – Critical bleeding/Massive transfusion*. NBA, Canberra, Australia.
- 5 McMahon LP and MacGinley R (2012). KHA-CARI guideline: biochemical and haematological targets: haemoglobin concentrations in patients using erythropoietin-stimulating agents. *Nephrology (Carlton)* 17(1):17-19.
<http://www.ncbi.nlm.nih.gov/pubmed/22044720>
- 6 National Blood Authority (NBA) (2012). *Patient blood management guidelines: Module 2 – Perioperative*. NBA, Canberra, Australia.
- 7 Baker RI, Coughlin PB, Gallus AS, Harper PL, Salem HH and Wood EM (2004). Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 181(9):492-497.
<http://www.ncbi.nlm.nih.gov/pubmed/15516194>
- 8 O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, et al. (2004). Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology* 126(1):11 – 28.
<http://www.ncbi.nlm.nih.gov/pubmed/15198728>
- 9 Anonymous (2003). Guidelines for the use of platelet transfusions. *British Journal of Haematology* 122(1):10-23.
<http://www.ncbi.nlm.nih.gov/pubmed/12823341>
- 10 National Blood Authority (NBA) (2012). *Technical report on medical patient blood management: Volume 1 – Review of the evidence*. NBA, Canberra, Australia.
- 11 National Blood Authority (NBA) (2012). *Technical report on medical patient blood management: Volume 2 – Appendixes*. NBA, Canberra, Australia.
- 12 National Health and Medical Research Council (NHMRC) (1999). *A guide to the development, implementation and evaluation of clinical practice guidelines*, NHMRC, Canberra, Australia.
<http://www.nhmrc.gov.au/publications/synopses/cp30syn.htm>
- 13 National Health and Medical Research Council (NHMRC) (2007). *NHMRC standards and procedures for externally developed guidelines*, NHMRC, Canberra, Australia.
<http://www.nhmrc.gov.au/publications/synopses/nh56syn.htm>

- 14 National Health and Medical Research Council (NHMRC) (2009). *NHMRC levels of evidence and grades for recommendations for developers of guidelines*, NHMRC, Canberra, Australia.
https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf
- 15 Anker SD, Voors A, Okonko D, Clark AL, James MK, von Haehling S, et al. (2009). Prevalence, incidence, and prognostic value of anaemia in patients after an acute myocardial infarction: Data from the OPTIMAAL trial. *European Heart Journal* 30(11):1331 – 1339.
- 16 Valeur N, Nielsen OW, McMurray JJV, Torp-Pedersen C and Kober L (2006). Anaemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. *European Journal of Heart Failure* 8(6):577 – 584.
- 17 Archbold RA, Balami D, Al-Hajiri A, Suliman A, Liew R, Cooper J, et al. (2006). Hemoglobin concentration is an independent determinant of heart failure in acute coronary syndromes: Cohort analysis of 2310 patients. *American Heart Journal* 152(6):1091 – 1095.
- 18 Aronson D, Suleiman M, Agmon Y, Suleiman A, Blich M, Kapeliovich M, et al. (2007). Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. *European Heart Journal* 28(11):1289 – 1296.
- 19 Giraldez RR, Sabatine MS, Morrow DA, Mohanavelu S, McCabe CH, Antman EM, et al. (2009). Baseline hemoglobin concentration and creatinine clearance composite laboratory index improves risk stratification in ST-elevation myocardial infarction. *American Heart Journal* 157(3):517 – 524.
- 20 Keough-Ryan TM, Kiberd BA, Dipchand CS, Cox JL, Rose CL, Thompson KJ, et al. (2005). Outcomes of acute coronary syndrome in a large Canadian cohort: Impact of chronic renal insufficiency, cardiac interventions, and anemia. *American Journal of Kidney Diseases* 46(5):845 – 855.
- 21 Sabatine MS, Morrow DA, Giugliano RP, Burton PBJ, Murphy SA, McCabe CH, et al. (2005). Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation* 111(16):2042 – 2049.
- 22 Bassand JP, Afzal R, Eikelboom J, Wallentin L, Peters R, Budaj A, et al. (2010). Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. *European Heart Journal* 31(1):50 – 58.
- 23 Burr ML, Holliday RM, Fehily AM and Whitehead PJ (1992). Haematological prognostic indices after myocardial infarction: Evidence from the diet and reinfarction trial (DART). *European Heart Journal* 13(2):166 – 170.
- 24 Mahaffey KW, Yang Q, Pieper KS, Antman EM, White HD, Goodman SG, et al. (2008). Prediction of one-year survival in high-risk patients with acute coronary syndromes: Results from the SYNERGY trial. *Journal of General Internal Medicine* 23(3):310 – 316.
- 25 Cavusoglu E, Chopra V, Gupta A, Clark LT, Eng C and Marmur JD (2006). Usefulness of anemia in men as an independent predictor of two-year cardiovascular outcome in patients presenting with acute coronary syndrome. *American Journal of Cardiology* 98(5):580 – 584.
- 26 Hasin T, Sorkin A, Markiewicz W, Hammerman H and Aronson D (2009). Prevalence and prognostic significance of transient, persistent, and new-onset anemia after acute myocardial infarction. *American Journal of Cardiology* 104(4):486 – 491.

- 27 Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. (2005). Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: Results from Val-HeFT. *Circulation* 112(8):1121 – 1127.
- 28 Baggish AL, van Kimmenade R, Bayes-Genis A, Davis M, Lainchbury JG, Frampton C, et al. (2007). Hemoglobin and N-terminal pro-brain natriuretic peptide: Independent and synergistic predictors of mortality in patients with acute heart failure. Results from the International Collaborative of NT-proBNP (ICON) study. *Clinica Chimica Acta* 381(2):145 – 150.
- 29 Ceresa M, Capomolla S, Pinna G, Aiolfi E, La Rovere MT, Febo O, et al. (2005). Anemia in chronic heart failure patients: Comparison between invasive and non-invasive prognostic markers. *Monaldi Archives for Chest Disease - Cardiac Series* 64(2):124-133.
- 30 Felker GM, Gattis WA, Leimberger JD, Adams K, Cuffe MS, Gheorghiade M, et al. (2003). Usefulness of anaemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *American Journal of Cardiology* 92:625 – 628.
- 31 Garty M, Shotan A, Gottlieb S, Mittelman M, Porath A, Lewis BS, et al. (2007). The management, early and one year outcome in hospitalized patients with heart failure: A national heart failure survey in Israel - HFSIS 2003. *Israel Medical Association Journal* 9(4):227 – 233.
- 32 Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Takeshita A, Yokoshiki H, et al. (2009). Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan: A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circulation Journal* 73(10):1901 – 1908.
<http://www.ncbi.nlm.nih.gov/pubmed/19652398>
- 33 Ingle L, Rigby AS, Carroll S, Butterly R, King RF, Cooke CB, et al. (2007). Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. *European Heart Journal* 28(5):560 – 568.
- 34 Kalra PR, Collier T, Cowie MR, Fox KF, Wood DA, Poole-Wilson PA, et al. (2003). Haemoglobin concentration and prognosis in new cases of heart failure. *Lancet* 362(9379):211 – 212.
- 35 Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A, et al. (2006). The impact of new onset anaemia on morbidity and mortality in chronic heart failure: Results from COMET. *European Heart Journal* 27(12):1440 – 1446.
- 36 Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, et al. (2005). Anemia in patients with heart failure: Prevalence and prognostic role in a controlled trial and in clinical practice. *Journal of Cardiac Failure* 11(2):91 – 98.
- 37 Maraldi C, Volpato S, Cesari M, Onder G, Pedone C, Woodman RC, et al. (2006). Anemia, physical disability and survival in older patients with heart failure. *Journal of Cardiac Failure* 12(7): 533 – 539.
- 38 Poole-Wilson PA, Uretsky BF, Thygesen K, Cleland JGF, Massie BM and Ryden L (2003). Mode of death in heart failure: Findings from the ATLAS trial. *Heart* 89(1):42 – 48.
- 39 Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, et al. (2008). Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF Registry). *American Journal of Cardiology* 101(2): 223 – 230.
- 40 Adams, Jr., Pina IL, Ghali JK, Wagoner LE, Dunlap SH, Schwartz TA, et al. (2009). Prospective evaluation of the association between hemoglobin concentration and quality of life in patients with heart failure. *American Heart Journal* 158(6):965 – 971.

- 41 Chaves PHM, Xue QL, Guralnik JM, Ferrucci L, Volpato S and Fried LP (2004). What constitutes normal hemoglobin concentration in community-dwelling disabled older women? *Journal of the American Geriatrics Society* 52(11):1811 – 1816.
- 42 Denny SD, Kuchibhatla MN and Cohen HJ (2006). Impact of anemia on mortality, cognition, and function in community-dwelling elderly. *American Journal of Medicine* 119(4):327 – 334.
- 43 Dong X, Mendes de Leon C, Artz A, Tang Y, Shah R and Evans D (2008). A population-based study of hemoglobin, race and mortality in elderly persons. *Journal of Gerontology: Medical Sciences* 63A(8):873 – 878.
- 44 Endres HG, Wedding U, Pittrow D, Thiem U, Trampisch HJ and Diehm C (2009). Prevalence of anemia in elderly patients in primary care: Impact on 5-year mortality risk and differences between men and women. *Current Medical Research and Opinion* 25(5):1143 – 1158.
<http://www.informapharmascience.com/doi/pdf/10.1185/03007990902860325>
- 45 Izaks GJ, Westendorp RGJ and Knook DL (1999). The definition of anemia in older persons. *Journal of the American Medical Association* 281(18):1714 – 1717.
- 46 Riva E, Tettamanti M, Mosconi P, Apolone G, Gandini F, Nobili A, et al. (2009). Association of mild anemia with hospitalization and mortality in the elderly: The Health and Anemia population-based study. *Haematologica* 94(1):22 – 28.
<http://www.haematologica.org/cgi/reprint/94/1/22>
- 47 Patel KV, Harris TB, Faulhaber M, Angleman SB, Connelly S, Bauer DC, et al. (2007). Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood* 109:4663 – 4670.
- 48 Patel KV, Longo DL, Ershler WB, Yu B, Semba RD, Ferrucci L, et al. (2009). Haemoglobin concentration and the risk of death in older adults: Differences by race/ethnicity in the NHANES III follow-up. *British Journal of Haematology* 145(4):514 – 523.
- 49 Penninx BWJH, Pahor M, Woodman RC and Guralnik JM (2006). Anemia in old age is associated with increased mortality and hospitalization. *Journal of Gerontology: Medical Sciences* 61A(5): 474 – 479.
- 50 Thein M, Ershler WB, Artz AS, Tecson J, Robinson BE, Rothstein G, et al. (2009). Diminished quality of life and physical function in community-dwelling elderly with anemia. *Medicine* 88(2):107 – 114.
- 51 Zakari NA, Katz R, Hirsch C, Shlipak MG, Chaves PHM, Newman AB, et al. (2005). A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: The cardiovascular health study. *Archives of Internal Medicine* 165(19):2214 – 2220.
<http://archinte.ama-assn.org/cgi/reprint/165/19/2214>
- 52 Lucca U, Tettamanti M, Mosconi P, Apolone G, Gandini F, Nobili A, et al. (2008). Association of mild anemia with cognitive, functional, mood and quality of life outcomes in the elderly: The "health and anemia" study. *PLoS ONE* 3(4): e1920.
<http://www.plosone.org/article/fetchObjectAttachment.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0001920&representation=PDF>
- 53 Armstrong AJ, Garrett-Mayer E, De Wit R, Tannock I and Eisenberger M (2010). Prediction of survival following first-line chemotherapy in men with castration-resistant metastatic prostate cancer. *Clinical Cancer Research* 16(1):203 – 211.
<http://clincancerres.aacrjournals.org/content/16/1/203.full.pdf+html>

- 54 Beer TM, Tangen CM, Bland LB, Hussain M, Goldman BH, DeLoughery TG, et al. (2006). The prognostic value of hemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: A multivariate analysis of southwest oncology group study 8894. *Cancer* 107(3):489 – 496.
- 55 Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, et al. (2006). Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. *Clinical Cancer Research* 12(11 I):3361 – 3367.
- 56 Halabi S, Vogelzang NJ, Ou SS, Owzar K, Archer L and Small EJ (2009). Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. *Journal of Clinical Oncology* 27(17):2766 – 2771.
- 57 Kohne CH, Cunningham D, Di Costanzo F, Glimelius B, Blijham G, Aranda E, et al. (2002). Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Annals of Oncology* 13:308–317.
- 58 Laurie SA, Ding K, Whitehead M, Feld R, Murray N, Shepherd FA, et al. (2007). The impact of anemia on outcome of chemoradiation for limited small-cell lung cancer: A combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. *Annals of Oncology* 18(6): 1051 – 1055.
- 59 Mandrekar SJ, Schild SE, Hillman SL, Allen KL, Marks RS, Mailliard JA, et al. (2006). A prognostic model for advanced stage nonsmall cell lung cancer: Pooled analysis of north central cancer treatment group trials. *Cancer* 107(4):781 – 792.
- 60 Negrier S, Escudier B, Gomez F, Douillard JY, Ravaud A, Chevreau C, et al. (2002). Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: A report from the Groupe Français d'Immunothérapie. *Annals of Oncology* 13(9): 1460 – 1468.
- 61 Nieboer P, Buijs C, Rodenhuis S, Seynaeve C, Beex LVAM, Van Der Wall E, et al. (2005). Fatigue and relating factors in high-risk breast cancer patients treated with adjuvant standard or high-dose chemotherapy: A longitudinal study. *Journal of Clinical Oncology* 23(33):8296 – 8304.
- 62 Osterlind K and Andersen PK (1986). Prognostic factors in small cell lung cancer: Multivariate model based on 778 patients treated with chemotherapy with or without irradiation. *Cancer Research* 46(8):4189 – 4194.
- 63 Paesmans M, Sculier JP, Libert P, Bureau G, Dabouis G, Thiriaux J, et al. (1995). Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1 052 patients. *Journal of Clinical Oncology* 13:1221–1230.
- 64 Paesmans M, Sculier JP, Lecomte J, Thiriaux J, Libert P, Sergysels R, et al. (2000). Prognostic factors for patients with small cell lung carcinoma: Analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. *Cancer* 89(3):523 – 533.
- 65 Wisloff F, Gulbrandsen N, Hjorth M, Lenhoff S and Fayers P (2005). Quality of life may be affected more by disease parameters and response to therapy than by haemoglobin changes. *European Journal of Haematology* 75(4):293 – 298.
- 66 Volkova N and Arab L (2006). Evidence-based systematic literature review of hemoglobin/ hematocrit and all-cause mortality in dialysis patients. *American Journal of Kidney Diseases* 47(1):24 – 36.

- 67 Abramson JL, Jurkowitz CT, Vaccarino V, Weintraub WS and McClellan W (2003). Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC study. *Kidney International* 64(2):610 – 615.
- 68 Astor BC, Coresh J, Heiss G, Pettitt D and Sarnak MJ (2006). Kidney function and anemia as risk factors for coronary heart disease and mortality: The atherosclerosis risk in communities (ARIC) study. *American Heart Journal* 151(2):492 – 500.
- 69 Avram MM, Blaustein D, Fein PA, Goel N, Chattopadhyay J and Mittman N (2003). Hemoglobin predicts long-term survival in dialysis patients: A 15-year single-center longitudinal study and a correlation trend between prealbumin and hemoglobin. *Kidney International, Supplement* 64(87):S6–S11.
- 70 Finkelstein FO, Story K, Firanek C, Mendelssohn D, Barre P, Takano T, et al. (2009). Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clinical Journal of the American Society of Nephrology* 4(1):33 – 38.
<http://cjasn.asnjournals.org/cgi/reprint/4/1/33>
- 71 Fort J, Cuevas X, Garcia F, Perez-Garcia R, Lladós F, Lozano J, et al. (2010). Mortality in incident haemodialysis patients: Time-dependent haemoglobin levels and erythropoiesis-stimulating agent dose are independent predictive factors in the ANSWER study. *Nephrology Dialysis Transplantation* 25(8):2702 – 2710.
- 72 Leeder SR, Mitchell P, Liew G, Rochtchina E, Smith W and Wang JJ (2006). Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related death: The Blue Mountains eye study. *Journal of the American Society of Nephrology* 17(1):279 – 284.
- 73 Plantinga LC, Fink NE, Jaar BG, Huang IC, Wu AW, Meyer KB, et al. (2007). Relation between level or change of hemoglobin and generic and disease-specific quality of life measures in hemodialysis. *Quality of Life Research* 16(5):755 – 765.
- 74 Portoles J, Lopez-Gomez JM and Aljama P (2007). A prospective multicentre study of the role of anaemia as a risk factor in haemodialysis patients: The MAR study. *Nephrology Dialysis Transplantation* 22(2):500 – 507.
- 75 Robinson BM, Joffe MM, Berns JS, Pisoni RL, Port FK and Feldman HI (2005). Anemia and mortality in hemodialysis patients: Accounting for morbidity and treatment variables updated over time. *Kidney International* 68(5):2323 – 2330.
- 76 Mollaoglu M (2004). Depression and health-related quality of life in hemodialysis patients. *Dialysis and Transplantation* 33(9):544 – 555.
- 77 Stevens LA, Djurdjev O, Cardew S, Cameron EC and Levin A (2004). Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: Evidence for the complexity of the association between mineral metabolism and outcomes. *Journal of the American Society of Nephrology* 15(3):770 – 779.
- 78 Turk S, Guney I, Altintepe L, Tonbul Z, Yildiz A and Yeksan M (2004). Quality of life in male hemodialysis patients: Role of erectile dysfunction. *Nephron – Clinical Practice* 96(1):c21–c27.
- 79 Yen TH, Lin JL, Lin-Tan DT and Hsu CW (2010). Association between body mass and mortality in maintenance hemodialysis patients. *Therapeutic Apheresis and Dialysis* 14(4):400 – 408.
- 80 Perlman RL, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, et al. (2005). Quality of life in chronic kidney disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study. *American Journal of Kidney Diseases* 45(4):658 – 666.

- 81 Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT, et al. (1997). Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. *American Journal of Kidney Diseases* 29(4):584 – 592.
- 82 Carless PA, Henry DA, Carson JL, Hébert PC, McLelland B and Ker K (2010). Tranfusion threshold and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database of Systematic Reviews* 2010(10):CD002042.
- 83 McMahon L (2008). The CARI Guidelines – Haemoglobin. *Nephrology* 13(s2):S44 – S56.
- 84 Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NMA, et al. (2008). Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. *American Heart Journal* 155(6):1047 – 1053.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L50082874>,
<http://dx.doi.org/10.1016/j.ahj.2008.01.009>
- 85 Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. (2004). Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *Journal of the American Medical Association* 292(13):1555 – 1562.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39314961>,
<http://dx.doi.org/10.1001/jama.292.13.1555>
- 86 Wu WC, Rathore SS, Wang Y, Radford MJ and Krumholz HM (2001). Blood transfusion in elderly patients with acute myocardial infarction. *New England Journal of Medicine* 345(17):1230 – 1236.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L34951486>
- 87 Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. (2004). Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 292(13):1555–1562. PM:15467057
- 88 Shishehbor MH, Madhwal S, Rajagopal V, Hsu A, Kelly P, Gurm HS, et al. (2009). Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction. *JACC: Cardiovascular Interventions* 2(1):46–53.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354071658>
<http://dx.doi.org/10.1016/j.jcin.2008.09.011>
- 89 Garty M, Cohen E, Zuchenko A, Behar S, Boyko V, Iakobishvili Z, et al. (2009). Blood transfusion for acute decompensated heart failure – friend or foe? *American Heart Journal* 158(4):653 – 658.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L355285461>,
<http://dx.doi.org/10.1016/j.ahj.2009.08.001>
- 90 Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA and Lyman GH (2008). Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. *Archives of Internal Medicine* 168(21):2377 – 2381.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L352743994>,
<http://archinte.ama-assn.org/cgi/reprint/168/21/2377>
- 91 Blair SD, Janvrin SB, McCollum CN and Greenhalgh RM (1986). Effect of early blood transfusion on gastrointestinal haemorrhage. *British Journal of Surgery* 73(10):783 – 785.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L16007117>

- 92 Hearnshaw SA, Logan RFA, Palmer KR, Card TR, Travis SPL and Murphy MF (2010). Outcomes following early red blood cell transfusion in acute upper gastrointestinal bleeding. *Alimentary Pharmacology and Therapeutics* 32(2):215 – 224.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L359041055>,
<http://dx.doi.org/10.1111/j.1365-2036.2010.04348.x>
- 93 Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, et al. (2010). Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust* 193(9): 525-532.
<http://www.ncbi.nlm.nih.gov/pubmed/21034387>
- 94 Tonelli M, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Lloyd A, et al. (2009). Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: A meta-analysis. *Canadian Medical Association Journal* 180(11):E62-E71.
<http://www.cmaj.ca/cgi/reprint/180/11/E62>
- 95 Hoskin PJ, Robinson M, Slevin N, Morgan D, Harrington K and Gaffney C (2009). Effect of epoetin alfa on survival and cancer treatment-related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. *Journal of Clinical Oncology* 27(34):5751 – 5756.
<http://jco.ascopubs.org/cgi/reprint/27/34/5751>
- 96 Tsuboi M, Ezaki K, Tobinai K, Ohashi Y and Saijo N (2009). Weekly administration of epoetin beta for chemotherapy-induced anemia in cancer patients: Results of a multicenter, phase III, randomized, double-blind, placebo-controlled study. *Japanese Journal of Clinical Oncology* 39(3):163 – 168.
- 97 Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, et al. (2006). Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *Journal of the National Cancer Institute* 98(10):708 – 714.
- 98 Auerbach M, Silberstein PT, Webb RT, Averyanova S, Ciuleanu TE, Shao J, et al. (2010). Darbepoetin alfa 300 or 500 (mu)g once every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *American Journal of Hematology* 85(9):655 – 663.
<http://onlinelibrary.wiley.com/doi/10.1002/ajh.21779/pdf>
- 99 Bastit L, Vandebroek A, Altintas S, Gaede B, Pint, r T, Suto TS, et al. (2008). Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *Journal of Clinical Oncology* 26:1611 – 1618.
- 100 Pedrazzoli P, Farris A, Del Prete S, Del Gaizo F, Ferrari D, Bianchessi C, et al. (2008). Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alfa. *Journal of Clinical Oncology* 26(10):1619 – 1625.
<http://jco.ascopubs.org/cgi/reprint/26/10/1619>
- 101 Hedenus M, Birgegard G, Nasman P, Ahlberg L, Karlsson T, Lauri B, et al. (2007). Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: A randomized multicenter study. *Leukemia* 21(4):627 – 632.

- 102 Dangsuwan P and Manchana T (2010). Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. *Gynecologic Oncology* 116(3):522 – 525.
- 103 Desai A, Lewis E, Solomon S, McMurray JJV and Pfeffer M (2010). Impact of erythropoiesis-stimulating agents on morbidity and mortality in patients with heart failure: An updated, post-TREAT meta-analysis. *European Journal of Heart Failure* 12(9):936 – 942.
- 104 Ngo K, Kotecha D, Walters JA, Manzano L, Palazzuoli A, van Veldhuisen DJ, et al. (2010). Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. *Cochrane Database of Systematic Reviews*(1):CD007613.
- 105 Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M, et al. (2008). Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency. FERRIC-HF: A randomized, controlled, observer-blinded trial. *Journal of the American College of Cardiology* 51(2):103 – 112.
- 106 Gandra SR, Finkelstein FO, Bennett AV, Lewis EF, Brazg T and Martin ML (2010). Impact of erythropoiesis-stimulating agents on energy and physical function in nondialysis CKD patients with anemia: A systematic review. *American Journal of Kidney Diseases* 55(3):519 – 534.
- 107 Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B and Manns B (2008). Erythropoiesis-stimulating agents for anemia of chronic kidney disease: Systematic review and economic evaluation (Structured abstract). *Canadian Agency for Drugs and Technologies in Health*:1.
- 108 Cody J, Daly C, Campbell M, Donaldson C, Khan I, Rabindranath K, et al. (2005). Recombinant human erythropoietin for chronic renal failure anaemia in pre-dialysis patients. *Cochrane Database of Systematic Reviews*(3):CD003266.
- 109 Johansen KL, Finkelstein FO, Revicki DA, Gitlin M, Evans C and Mayne TJ (2010). Systematic review and meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with erythropoiesis-stimulating agents. *American Journal of Kidney Diseases* 55(3):535 – 548.
- 110 Strippoli GF, Navaneethan SD and Craig JC (2006). Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *Cochrane Database of Systematic Reviews*(4):CD003967.
<http://www.ncbi.nlm.nih.gov/pubmed/17054191>
- 111 Macdougall IC, Temple RM and Kwan JTC (2007). Is early treatment of anaemia with epoetin-(alpha) beneficial to pre-dialysis chronic kidney disease patients? Results of a multicentre, open-label, prospective, randomized, comparative group trial. *Nephrology Dialysis Transplantation* 22(3):784 – 793.
- 112 Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, De Zeeuw D, Eckardt KU, et al. (2009). A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *The New England Journal of Medicine* 361:2019–2032.
- 113 Churchill D, Keown P, Laupacis A, Muirhead N, Sim D, Slaughter D, et al. (1990). Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *British Medical Journal* 300(6724):573 – 578.
- 114 Keown PA, Churchill DN, Poulin-Costello M, Lei L, Gantotti S, Agodoa I, et al. (2010). Dialysis patients treated with Epoetin alfa show improved anemia symptoms: A new analysis of the Canadian Erythropoietin Study Group trial. *Hemodialysis International* 14(2):168 – 173.

- 115 Cianciaruso B, Ravani P, Barrett BJ, Levin A, Torraca S, Procaccini DA, et al. (2008). Italian randomized trial of hemoglobin maintenance to prevent or delay left ventricular hypertrophy in chronic kidney disease. *Journal of Nephrology* 21(6):861 – 870.
<http://www.ncbi.nlm.nih.gov/pubmed/19034870>
- 116 Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O and Gafter U (2008). Intravenous versus oral iron supplementation for the treatment of anemia in CKD: Systematic review and meta-analysis. *American Journal of Kidney Diseases* 52(5):897 – 906.
- 117 Provenzano R, Schiller B, Rao M, Coyne D, Brenner L and Pereira BJG (2009). Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clinical Journal of the American Society of Nephrology* 4(2):386 – 393.
<http://cjasn.asnjournals.org/cgi/reprint/4/2/386>
- 118 Stoves J, Inglis H and Newstead CG (2001). A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrology Dialysis Transplantation* 16(5):967 – 974.
- 119 Van Wyck DB, Roppolo M, Martinez CO, Mazey RM and McMurray S (2005). A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney International* 68:2846 – 2856.
- 120 Singh H, Reed J, Noble S, Cangiano JL and Van Wyck DB (2006). Effect of intravenous iron sucrose in peritoneal dialysis patients who receive erythropoiesis-stimulating agents for anemia: A randomized, controlled trial. *Clinical Journal of the American Society of Nephrology* 1(3):475 – 482.
- 121 Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ and Besarab A (2006). A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *American Journal of Nephrology* 26(5):445 – 454.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L44971735>
- 122 Agnihotri P, Telfer M, Butt Z, Jella A, Cella D, Kozma CM, et al. (2007). Chronic anemia and fatigue in elderly patients: Results of a randomized, double-blind, placebo-controlled, crossover exploratory study with epoetin alfa. *Journal of the American Geriatrics Society* 55(10):1557 – 1565.
- 123 Kulnigg S, Stoinov S, Simanekov V, Dudar LV, Karnafel W, Garcia LC, et al. (2008). A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: The ferric carboxymaltose (FERINJECT – registered trademark) randomized controlled trial. *American Journal of Gastroenterology* 103(5):1182–1192.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351677967>
- 124 Schroder O, Mickisch O, Seidler U, De Weerth A, Dignass AU, Herfarth H, et al. (2005). Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease: A randomized, controlled, open-label, multicenter study. *American Journal of Gastroenterology* 100(11):2503 – 2509.
- 125 Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, et al. (2009). Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: Results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). *Blood* 114(12):2393 – 2400.
<http://bloodjournal.hematologylibrary.org/cgi/reprint/114/12/2393>

- 126 Thompson JA, Gilliland DG, Prchal JT, Bennett JM, Larholt K, Nelson RA, et al. (2000). Effect of recombinant human erythropoietin combined with granulocyte/macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. *Blood* 95(4):1175 – 1179.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L30099823>
- 127 Ferrini PR, Grossi A, Vannucchi AM, Barosi G, Guarnone R, Piva N, et al. (1998). A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. *British Journal of Haematology* 103(4): 1070 – 1074.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L29012646>
- 128 Leese T, Holliday M, Heath D, Hall AW and Bell PRF (1987). Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. *British Journal of Surgery* 74(10):907 – 911.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L18010985>
- 129 Leese T, Holliday M, Watkins M, Neoptolemos JP, Thomas WM, Attard A, et al. (1991). A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. *Annals of the Royal College of Surgeons of England* 73(4):207 – 214.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L21235231>
- 130 Gazzard BG, Henderson JM and Williams R (1975). The use of fresh frozen plasma or a concentrate of factor IX as replacement therapy before liver biopsy. *Gut* 16(8):621 – 625.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L6135493>
- 131 Solomon J, Bofenkamp T, Fahey JL, Chillar RK and Beutel E (1978). Platelet prophylaxis in acute non-lymphoblastic leukaemia. *Lancet* 1:267.
- 132 McCullough J, Vesole DH, Benjamin RJ, Slichter SJ, Pineda A, Snyder E, et al. (2004). Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: The SPRINT trial. *Blood* 104(5):1534 – 1541.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39166535>
- 133 Higby DJ, Cohen E, Holland JF and Sinks L (1974). The prophylactic treatment of thrombocytopenic leukemic patients with platelets: A double blind study. *Transfusion* 14(5):440 – 446.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L5164451>
- 134 Heim D, Passweg J, Gregor M, Buser A, Theodorides A, Arber C, et al. (2008). Patient and product factors affecting platelet transfusion results. *Transfusion* 48(4):681 – 687.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351430354>
- 135 Osselaer JC, Messe N, Hervig T, Bueno J, Castro E, Espinosa A, et al. (2008). A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. *Transfusion* 48(6):1061 – 1071.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351793479>
- 136 Slichter SJ (1997). Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *New England Journal of Medicine* 337(26):1861 – 1869.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L28053025>

- 137 Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al. (2010). Dose of prophylactic platelet transfusions and prevention of hemorrhage. *New England Journal of Medicine* 362(7):600 – 613.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L358334244>
- 138 Heddle NM, Cook RJ, Tinmouth A, Kouroukis CT, Hervig T, Klapper E, et al. (2009). A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood* 113(7):1564 – 1573.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L354286700>
- 139 Tinmouth A, Tannock IF, Crump M, Tomlinson G, Brandwein J, Minden M, et al. (2004). Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: A randomized controlled trial with a sequential Bayesian design. *Transfusion* 44(12):1711 – 1719.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L39644055>
- 140 Goodnough LT, Kuter DJ, McCullough J, Slichter SJ, DiPersio J, Romo J, et al. (2001). Prophylactic platelet transfusions from healthy apheresis platelet donors undergoing treatment with thrombopoietin. *Blood* 98(5):1346 – 1351.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L35119599>
- 141 Sensebé L, Giraudeau B, Bardiaux L, Deconinck E, Schmidt A, Bidet ML, et al. (2005). The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: Results of a prospective, randomized, open, blinded end point (PROBE) study. *Blood* 105(2):862 – 864.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L40070776>
- 142 Garden OJ, Motyl H and Gilmour WH (1985). Prediction of outcome following acute variceal haemorrhage. *British Journal of Surgery* 72(2):91 – 95.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L15170120>
- 143 Violi F, Ferro D, Basili S, Cimminiello C, Saliola M, Vezza E, et al. (1995). Prognostic value of clotting and fibrinolytic systems in a follow-up of 165 liver cirrhotic patients. *Hepatology* 22(1):96 – 100.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L25231490>
- 144 Kim H, Lee JH, Choi SJ, Seol M, Lee YS, Kim WK, et al. (2006). Risk score model for fatal intracranial hemorrhage in acute leukemia. *Leukemia* 20(5):770 – 776.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L43630916>
- 145 Dally N, Hoffman R, Haddad N, Sarig G, Rowe JM and Brenner B (2005). Predictive factors of bleeding and thrombosis during induction therapy in acute promyelocytic leukemia: A single center experience in 34 patients. *Thrombosis Research* 116(2):109 – 114.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L40720186>
- 146 Levi M, Toh CH, Thachil J and Watson HG (2009). Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *British Journal of Haematology* 145(1):24 – 33. PM:19222477
- 147 Rebullà P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, et al. (1997). The threshold for prophylactic platelet transfusion in adults with acute myeloid leukemia. *New England Journal of Medicine* 337:1870 – 1875.

- 148 Heckman KD, Weiner GJ, Davis CS, Strauss RG, Jones MP and Burns CP (1997). Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10 000/microL versus 20 000/microL. *Journal of Clinical Oncology* 15:1143 – 1149.
- 149 Zumberg MS, Del Rosario MLU, Nejame CF, Pollock BH, Garzarella L, Kao KJ, et al. (2002). A prospective randomized trial of prophylactic platelet transfusion and bleeding incidence in hematopoietic stem cell transplant recipients: 10 000/(mu)L versus 20 000/(mu)L trigger. *Biology of Blood and Marrow Transplantation* 8(10):569 – 576.
- 150 Diedrich B, Remberger M, Shanwell A, Svahn BM and Ringden O (2005). A prospective randomized trial of a prophylactic platelet transfusion trigger of 10 109 per L versus 30 109 per L in allogeneic hematopoietic progenitor cell transplant recipients. *Transfusion* 45:1064 – 1072.
- 151 Roudbari M, Soltani-Rad M and Roudbari S (2008). The survival analysis of beta thalassemia major patients in south east of Iran. *Saudi Medical Journal* 29(7):1031 – 1035.
<http://www.smj.org.sa/PDFFiles/Jul08/19Survival20071262.pdf>
- 152 Masera G, Terzoli S and Avanzini A (1982). Evaluation of the supertransfusion regimen in homozygous beta-thalassaemia children. *British Journal of Haematology* 52(1):111 – 113.
- 153 Torcharus K, Withayathawornwong W, Sriphaisal T, Krutvacho T, Arnutti P and Suwanasophorn C (1993). High transfusion in children with beta-thalassemia/Hb E: Clinical and laboratory assessment of 18 cases. *The Southeast Asian Journal of Tropical Medicine and Public Health* 24 Suppl 1:96 – 99.
- 154 Cazzola M, Borgna-Pignatti C, Locatelli F, Ponchio L, Beguin Y and De Stefano P (1997). A moderate transfusion regimen may reduce iron loading in (beta)-thalassemia major without producing excessive expansion of erythropoiesis. *Transfusion* 37(2):135 – 140.
- 155 Jansen AJG, Essink-Bot ML, Beckers EAM, Hop WCJ, Schipperus MR and Van Rhenen DJ (2003). Quality of life measurement in patients with transfusion-dependent myelodysplastic syndromes. *British Journal of Haematology* 121(2):270 – 274.
- 156 Vaupel P, Thews O and Hoeckel M (2001). Treatment resistance of solid tumors: Role of hypoxia and anemia. *Medical Oncology* 18(4):243 – 259. PM:11918451
- 157 Silva P, Homer JJ, Slevin NJ, Musgrove BT, Sloan P, Price P, et al. (2007). Clinical and biological factors affecting response to radiotherapy in patients with head and neck cancer: A review. *Clinical Otolaryngology* 32(5):337 – 345. PM:17883552
- 158 Aebersold DM, Burri P, Beer KT, Laissue J, Djonov V, Greiner RH, et al. (2001). Expression of hypoxia-inducible factor-1alpha: A novel predictive and prognostic parameter in the radiotherapy of oropharyngeal cancer. *Cancer Research* 61(7):2911 – 2916.
- 159 Knight K, Wade S and Balducci L (2004). Prevalence and outcomes of anemia in cancer: A systematic review of the literature. *American Journal of Medicine* 116(7, Supplement 1):11 – 26.
- 160 Van Belle SJ and Cocquyt V (2003). Impact of haemoglobin levels on the outcome of cancers treated with chemotherapy. *Critical Reviews in Oncology/Hematology* 47(1):1 – 11. PM:12853095
- 161 Grau C and Overgaard J (2000). Significance of haemoglobin concentration for treatment outcome. In: *Blood perfusion and microenvironment of human tumors: Implications for clinical radiooncology*, Molls M and Vaupel P (eds), Springer-Verlag, Berlin, 101 – 112.
- 162 Dunphy FR, Harrison BR, Dunleavy TL, Rodriguez JJ, Hilton JG and Boyd JH (1999). Erythropoietin reduces anemia and transfusions: A randomized trial with or without erythropoietin during chemotherapy. *Cancer* 86(7):1362 – 1367. PM:10506726

- 163 Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, et al. (2003). Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 362(9392):1255 – 1260. PM:14575968
- 164 Lambin P, Ramaekers BL, van Mastrigt GA, Van den Ende P, de JJ, De Ruyscher DK, et al. (2009). Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. *Cochrane Database Systematic Review*(3):CD006158. PM:19588382
- 165 Thomas G, Ali S, Hoebbers FJ, Darcy KM, Rodgers WH, Patel M, et al. (2008). Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecologic Oncology* 108(2):317 – 325. PM:18037478
- 166 Bush RS, Jenkin RD, Allt WE, Beale FA, Bean H, Dembo AJ, et al. (1978). Definitive evidence for hypoxic cells influencing cure in cancer therapy. *Br.J.Cancer Suppl* 3:302–306. PM:277250
- 167 Hoff CM, Hansen HS, Overgaard M, Grau C, Johansen J, Bentzen J, et al. (2011). The importance of haemoglobin level and effect of transfusion in HNSCC patients treated with radiotherapy – results from the randomized DAHANCA 5 study. *Radiotherapy and Oncology* 98(1):28 – 33. PM:20970213
- 168 Santin AD, Bellone S, Palmieri M, Bossini B, Dunn D, Roman JJ, et al. (2002). Effect of blood transfusion during radiotherapy on the immune function of patients with cancer of the uterine cervix: Role of interleukin-10. *International Journal of Radiation Oncology Biology Physics* 54(5):1345 – 1355. PM:12459356
- 169 Dzik WH (2003). Apoptosis, TGF beta and transfusion-related immunosuppression: Biologic versus clinical effects. *Transfus.Apher.Sci.* 29(2):127–129. PM:12941349
- 170 Blobel GC, Schiemann WP and Lodish HF (2000). Role of transforming growth factor beta in human disease. *N.Engl.J.Med.* 342(18):1350–1358. PM:10793168
- 171 Varlotto J and Stevenson MA (2005). Anemia, tumor hypoxemia, and the cancer patient. *International Journal of Radiation Oncology Biology Physics* 63(1):25 – 36. PM:16111569
- 172 Klein H and Lipton K (2001). *Non-infectious serious hazards of transfusion*. American Association of Blood Banks – Association Bulletin.
- 173 Knowles S, Cohen H and Serious Hazards of Transfusion Steering Group (2011). *The 2010 annual SHOT report*, Serious Hazards of Transfusion (SHOT).
<http://www.shotuk.org/wp-content/uploads/2011/10/SHOT-2010-Report1.pdf>
- 174 Wiesen AR, Hospenthal DR, Byrd JC, Glass KL, Howard RS and Diehl LF (1994). Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. *Ann Intern Med* 121(4):278–230.
<http://www.ncbi.nlm.nih.gov/pubmed/8037410>
- 175 Snyder-Ramos SA, Mohnle P, Weng YS, Bottiger BW, Kulier A, Levin J, et al. (2008). The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion* 48(7):1284 – 1299.
<http://www.ncbi.nlm.nih.gov/pubmed/18422857>
- 176 Australian Commission on Safety and Quality in Health Care (ACSQHC) (2011). *National safety and quality health service standards*, ACSQHC, Sydney.

- 177 Calman K (1996). The Health of the Nation. *British Journal of Hospital Medicine* 56(4):125 – 126.
<http://www.ncbi.nlm.nih.gov/pubmed/8872334>
- 178 National Health and Medical Research Council (NHMRC) (2000). *How to use the evidence: assessment and application of scientific evidence*. NHMRC handbook series, NHMRC, Canberra, Australia.
<http://www.nhmrc.gov.au/publications/synopses/cp69syn.htm>

ARCHIVED

Index

A

abbreviations, iii–iv
abciximab, 56
Aboriginal communities, 27, 73
acquired hypofibrinogenaemia, 57
acquired immunodeficiency syndrome patients, 49
acronyms, iii–iv
action-oriented recommendations, 24
acute coronary syndrome
 anaemia and, 28–9
 patients with, 7, 49
 RBC transfusions and, 34–5
 recommendations and practice points, 105
acute haemolytic reactions, 88
acute myocardial infarction, anaemia and, 29
acute pancreatitis, 50–1
acute promyelocytic leukaemia, 56–8
acute upper gastrointestinal blood loss, 8, 37, 110
admission prothrombin ratio, 56
AHCD guidelines, 10–11
allogeneic haematopoietic stem cell transplantation, 57–9, 113–14
anaemia
 aplastic, 12
 cancer patients with, 3, 66
 CKD patients with, 4
 effect on outcomes, 28–31
 in myelodysplasia, 62
 iron deficiency anaemia, 7, 105, 113
 optimising tolerance to, 15
 refractory anaemia with ringed sideroblasts, 49
 relieving signs of, 5
anaphylactoid reactions to transfusion, 88
antifibrinolytics, 73
aplastic anaemia, 12
Australian blood sector, 92–3
Australian Commission on Safety and Quality in Healthcare, 76
Australian Health Ministers' Advisory Council, 92
Australian Red Cross Blood Service, 93, 101

B

background material, 23, 65–9, 83
bacterial sepsis, 88
beta-thalassaemia major, *see* thalassaemia patients
bladder cancers, 67
bleeding events, *see* blood loss
blood component transfusions, 50–9
blood loss, *see also* acute upper gastrointestinal blood loss; critical bleeding
 minimisation of, 15
blood sectors, 91–5
BloodSafe eLearning program, 76
body of evidence matrix, 25
bronchial cancers, 67

C

Calman Chart, 88–9
cancer patients, *see also* chemotherapy patients
 anaemia and, 7–8, 30–1, 39–40
 ESA therapy and, 39–41
 haemoglobin levels, 66–7
 RBC transfusions and, 8, 36
 recommendations and practice points, 3, 108–9
Caring for Australasians with Renal Impairment guidelines, 8, 33
cerebrovascular disease patients, 49
cervical cancers, 67
chelation therapy, 60–1
chemotherapy patients
 anaemia in, 39–40
 platelet transfusions for, 4, 12, 53, 57–8
 recommendations and practice points, 113–14
 with leukaemia, 57
chronic heart failure, 3, 42–3
chronic kidney disease
 anaemia and, 31
 ESA therapy, 8
 ESA therapy and, 3–4, 44, 46
 iron therapy and, 45–7
 recommendations and practice points, 111–12

chronically transfused patients, 60–2
 Clinical, Technical and Ethical Principle Committee, 92
 clinical practice guidance, 17–18, 27–63
Clinical Practice Guidelines on the Use of Blood Components, 16, 60, 98
 clinical research questions, 22
 Clinical/Consumer Reference Groups, 1, 17, 80–1, 83
 coagulation parameters, 56
 coagulopathy, 9–10, 52, 116
 Cochrane reviews, 33
 Colitis Activity Index, 48
 community-dwelling elderly, 30
 conflict of interest declaration, 85
 Creutzfeldt–Jakob disease, transfusion risk of, 90
 critical bleeding, *see also* acute haemolytic reactions
 chemotherapy patients, 58
 guidelines for management, 8, 37
 heparinised patients, 56
 management of, 73
 platelet transfusions and, 12, 54
 Crohn's Disease Activity Index, 48
 cryoprecipitate, 11, 52, 116
 cytopenias, 62

D

darbepoetin, 41
 desferrioxamine, 61
 development process, 98
 diabetes, patients with, 44, 111

E

elderly patients, 30, 47
 end-stage kidney disease, 38, *see also* chronic kidney disease
 erythropoiesis-stimulating agent therapy
 cancer patients, 67, 109
 chronic kidney disease patients, 3, 8, 111
 effects of, 38–49
 gastrointestinal conditions, 110
 heart failure and, 106
 erythropoietin, 38, 41
 European Organization for Research and Treatment of Cancer Quality Questionnaire, 31
 evaluating guidelines, 75–6
 evidence, gaps in, 72

evidence statements, development of, 24–5
 executive summary, 1
 Expert Working Group, 17, 80–2

F

fibrinogen concentrate
 as alternative to cryoprecipitate, 73
 effects of, 52
 for leukaemia patients, 57
 for liver disease patients, 57
 guidelines for use of, 11
 recommendations and practice points, 116
 Food and Drug Administration (US), 46
 fresh frozen plasma transfusions, 9, 50–1, 116
 Functional Assessment of Cancer Therapy, 41
 functional iron deficiency, 38
 future directions, 71–2

G

gastrointestinal conditions, recommendations and practice points, 109–10
 general medical recommendations and practice points, 104
 governance of blood management guidelines, 17, 79–85
 grading scheme for recommendations, 2, 25
 graft-versus-host disease, as transfusion risk, 90
 granulocyte/macrophage colony-stimulating factor therapy, 49
 guidelines
 application of, 75–6
 finalising, 99
Guidelines for the diagnosis and management of disseminated intravascular coagulation, 57
Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant, 10–11
 gynaecological cancer patients, 40
 Gynecologic Oncology Group, 67

H

haematopoietic stem cell transplantation, 57–9, 113–14
 haemoglobin levels, raising, 66–7
 haemorrhage, *see* critical bleeding
 haemostasis, improving, 55
 haematological malignancies, 53–4
 haematopoietic stem cell transplantation patients, 4, 12

Hb levels, 29, 104
 head and neck cancers, 67
 heart failure
 anaemia and, 29
 ESA therapy and, 42–3
 iron therapy and, 42–3
 RBC transfusions and, 35
 recommendations and practice points, 3, 106–7
 risk of circulatory overload, 7
 heparinised patients, 56
 hepatic conditions, *see also* liver disease
 as transfusion risk, 88
 hepatitis patients, 49
 human immunodeficiency virus, 49
 as transfusion risk, 88
 human leukocyte antigen, 60
 human T-lymphotropic virus, as transfusion risk, 88
 hypersplenism, 61
 hypoxia-inducible factor family, 66

I
 immunomodulation, as transfusion risk, 90
 immunosuppression, 67
 implementing guidelines, 75–6
 inclusion criteria, 98
 independent systematic review expert, 80, 84
 inflammatory bowel disease, 9, 48–9
 informed consent, 15
 intravenous iron therapy, 9, 40–1, 46–7
 iron deficiency
 anaemia due to, 7, 105, 113
 functional, 38
 in CHF patients, 3
 iron therapy
 cancer patients, 109
 chelation therapy, 28
 chronic kidney disease, 111
 effects of, 38–49
 gastrointestinal conditions, 110
 heart failure and, 106
 intravenous, 40–1, 46–7
 oral, 40–1

J
 Jurisdictional Blood Committee, 76, 80, 92

K
 Kansas City Cardiomyopathy Questionnaire, 29

L
 leukaemia, treatment for, 56–8
 liver disease, patients with, 49, 50–1, 56–7

M
 maintaining guidelines, 75–6
 malaria, transfusion risk, 90
 malignancies, patients with, 66–7, *see also* cancer patients
 management framework, 80
 Medsafe (NZ), 93
 membership of governance bodies, 82–4
 metastatic prostate cancer, 31
 methodology, 21–6, 98
 Ministry of Health (NZ), 93
 Minnesota Living with Heart Failure Questionnaire, 29
 myelodysplasia, patients with
 ESA therapy and, 49
 recommendations and practice points, 115
 red blood cell transfusions, 60, 62
 transfusion thresholds, 12–13
 myelosuppressive chemotherapy, 59

N
 National Blood Authority, 92–3
National Safety and Quality Health Service Standards, 76
 New Zealand blood sector, 93
 New Zealand Blood Service, 93–4, 101
 NHMRC grading levels, 2, 25
 non-myeloid malignancies, 40

O
 optimisation of blood volume, 15
 OptumInsight, 84
 oral iron therapy, 40–1

P
 pancreatitis, patients with, 50–1
 paracetamol overdose, 51
Patient Blood Management Guidelines, 10–11, 33–4

Pharmaceutical Benefits Scheme, 41
platelet transfusions
 chemotherapy patients, 57–8, 114
 effects of, 53–5
 for bleeding, 12
 haematopoietic stem cell transplantation and, 114
 indications for, 11
 myelodysplasia patients, 115
 prophylactic use, 4
 thalassaemia patients, 115
 thrombocytopenia and, 117
practice points, 5–13, 17, 24–5
process report, 97–9
product information, 101
public consultation, 99

Q

quality of life, 29, 31, 46–7, 61

R

radiotherapy patients, 49, 66–7
recommendations, 3–4, 17, 24–5
red blood cell transfusions
 acute coronary syndrome patients, 7
 assessment of results, 68
 cancer patients, 8, 67, 108–9
 chemotherapy patients, 113
 chronic kidney disease patients, 111–12
 chronically transfused patients, 60–2
 effect on outcomes, 32–7
 gastrointestinal conditions, 109–10
 general medical recommendations and practice points, 104
 haematopoietic stem cell transplantation, 113
 heart failure and, 106–7
 indications for, 5–6
 myelodysplasia patients, 115
 thalassaemia patients, 115
references, 119–34
refractory anaemia with ringed sideroblasts, 49
related materials, 18
renal failure, anaemia and, 31, *see also* chronic kidney disease
research, 22–3, 98
respiratory disease patients, 49
retesting of patients, 68

S

serum ferritin levels, 38
Short Form-36, 31, 48
sickle cell disease, 60
specific factor deficiencies, 10
splenectomy, 61
Standing Committee on Health, 92
Steering Committee, 17, 80–2
sudden cardiac death, anaemia and, 29
summary of recommendations and practice points, 2–13, 103–17
Symptoms and Effects of CKD on Kidney Disease Quality of Life Questionnaire, 47
systematic reviews, 17, 22–3, 80–1, 84

T

terms of reference, 80–1
thalassaemia patients, 13, 60–2, 73, 115
Therapeutic Goods Administration, 93
thrombocytopenia, 11, 54, 117
thromboembolic events, 39, 41, 53, 67
Torres Strait Islander communities, 27, 73
transfusion triggers, 55
transfusion-associated circulatory overload, 7, 35, 88
transfusion-related acute lung injury, 88
tumour hypoxia, 66–7

W

Warfarin Reversal: Consensus Guidelines, 10
World Health Organization, on anaemia, 2

ARCHIVED