

Diagnosis and management of iron deficiency anaemia

Interview with **Dr Kathryn Robinson** MB BS, FRACP, FRCPA, Transfusion Medicine Specialist and Haematologist. Australian Red Cross Blood Service, Adelaide, SA; The Queen Elizabeth Hospital, Adelaide, South Australia

Q Iron deficiency anaemia is a common disorder, particularly in at risk groups. It may also indicate important underlying pathology such as asymptomatic gastrointestinal cancer. What are some of the challenges with diagnosis?

A First of all, iron deficiency needs to be distinguished from other causes of anaemia. This can be achieved, in most cases, by a full blood count and serum ferritin level. Ferritin is the most readily available and useful indicator of iron status. However, it is important to be aware that ferritin is also an acute-phase reactant and is misleadingly elevated in inflammation, infection, liver disease and malignancy. C-reactive protein can be useful to help identify coexisting inflammation. Serum iron should **not** be used to diagnose iron deficiency. When the diagnosis is unclear, guidance should be sought from a pathologist or other relevant expert.

Once iron deficiency anaemia has been diagnosed, the cause needs to be established in all patients. Management involves two *concurrent* components: determination and treatment of the underlying cause (e.g. bleeding) and iron therapy to normalise the haemoglobin and replenish iron stores. In patients without a clear physiological explanation for iron deficiency (especially men and postmenopausal women), evaluation by

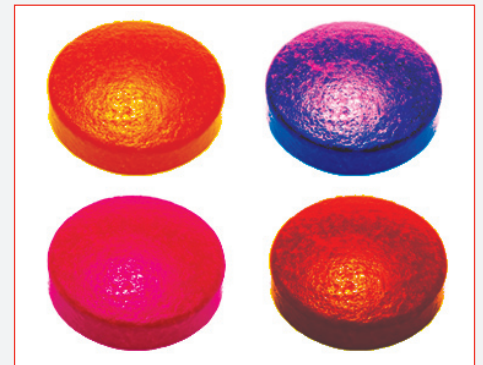
gastroscopy/colonoscopy to exclude a source of gastrointestinal bleeding, particularly a malignant lesion, is a priority.

Oral iron therapy is an effective first line strategy for most patients provided it is given in appropriate doses and for a sufficient duration. What are some of the issues with its use?

While there are more than 100 iron-containing preparations available over the counter, few contain sufficient elemental iron to provide a therapeutic dose. Clinicians should write the name of the preparation recommended for the patient to take to the pharmacist. Advice regarding how to take the iron should be given along with appropriate storage (out of reach of children to avoid accidental ingestion which can be fatal). If gastrointestinal upset is a problem, the dose can be taken with food or at night. Gastrointestinal upset is generally dose-related so lower daily doses or intermittent dosing (2–3 times per week) can be effective strategies, especially when a rapid increase in haemoglobin level is not clinically important.

Is dietary therapy effective in the treatment of iron deficiency anaemia?

Increasing dietary intake alone is inadequate to treat frank iron deficiency anaemia, but may be valuable for secondary prevention.



What is the role of intravenous versus oral iron in the management of iron deficiency anaemia?

Oral iron is the cornerstone of therapy for iron deficiency anaemia, an effective first line strategy for most patients provided the dose and duration are adequate. Adequate doses of oral iron (100–200 mg of elemental iron per day in adults) can raise the haemoglobin level by around 20 g/L in a few weeks. This is equivalent to two units of red cells. Oral iron, however, cannot cover the needs of all patients, and intravenous iron is sometimes required in selected patients, in consultation with a specialist.

Current intravenous iron preparations can be safely administered in day-patient treatment centres and are relatively inexpensive. In patients with iron deficiency anaemia, intravenous iron can provide rapid iron repletion when this is clinically important, such as to prevent decompensation or transfusion (and its associated hazards). Timely consultation with a relevant expert is needed to ensure

continued overleaf

DISCLAIMER This newsletter has been prepared by Transfusion Medicine Services at the Australian Red Cross Blood Service, a division of the Australian Red Cross Society. Every endeavour has been made to ensure the contents are correct and accurate at the time of publication, however, the medical environment is constantly changing and information herein may become out of date. The information in this publication is provided as a general guide only and should not be used to replace professional advice.

In this issue

- Impact of albumin compared to saline for patients with sepsis
- Biostate® advisory statement
- Updated risk estimates for transfusion-transmitted infections
- Register for Transfusion Update 2011

unnecessary transfusion is avoided and appropriate iron therapy is provided. The use of intramuscular iron is discouraged.

Uncertainty about when and how to administer intravenous iron preparations is an important contributor to under-utilisation in patients with indications for its use. This was an important area where a clinical update was needed, particularly specific to the Australian context.

In a recent article published in the *Medical Journal of Australia*¹, you stated that transfusion of red cells remains an overused treatment for iron deficiency anaemia. Can you elaborate on this?

Suboptimal identification, investigation and management of iron deficiency anaemia is an important contributor to unnecessary and reflex decisions to transfuse. In compensated patients who do not require an immediate increase in oxygen carrying capacity, transfusion carries unnecessary risks and fails to replenish deficient iron stores. If transfusion is required (e.g. for cardiac compromise or in the setting of serious acute blood loss), it is still important to ensure that iron therapy is given. ■

Reference

1. Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, Roger SD, Savoia HF, Tampi R, Thomson AR, Wood EM, Robinson KL. Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust* 2010;193(9): 525–32.

The authors of this paper are members of the Australian Iron Deficiency Expert Group, comprising health professionals from diverse backgrounds with a shared interest in alleviating the burden and optimising management of iron deficiency anaemia in Australia. Formation of the expert group was an initiative of the Australian and New Zealand Society of Blood Transfusion, supported by the Australian Red Cross Blood Service, New South Wales Clinical Excellence Commission (Blood Watch program), Victorian Department of Health (Blood Matters program) and South Australian Department of Health (BloodSafe program). During a meeting in May 2009, the expert group conducted a barrier analysis around improving the diagnosis and management of iron deficiency anaemia in Australia. Many common clinical misconceptions were identified and, thus, developing a national education strategy was given high priority. A writing group was formed to provide a clinical update specific for the Australian setting.

The article includes useful tables and figures related to interpretation of iron indices, assessment and management of iron deficiency, iron preparations and dosing, causes of suboptimal response to oral iron and indications for intravenous iron. Other useful tools and resources related to anaemia management can be found at www.health.sa.gov.au/bloodsafe (SA Department of Health website for Bloodsafe).

Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis

A new study¹ has reported albumin compared to saline did not impair renal or other organ function and may have decreased the risk of death among severe sepsis patients requiring fluid resuscitation. Published in the journal *Intensive Care Medicine*, this new study from the SAFE Study investigators is a follow-up analysis of the pre-defined cohort of patients with severe sepsis from the 2004 SAFE study².

The 2004 SAFE study², a prospective, double-blind randomised controlled trial, was conducted among 6997 intensive care unit (ICU) patients (≥ 18 years) from 16 hospitals in Australia and New Zealand. The study compared the effects of fluid resuscitation with albumin 4% to saline on the mortality of a large and diverse group of patients. The primary outcome was all-cause mortality within 28 days of randomisation, and patients were followed until death, discharge or 28 days post-randomisation. Secondary outcomes were the survival time during the first 28 days, the proportion of patients who had new organ failures, length of stay in the ICU, length of stay in hospital, duration of mechanical ventilation and duration of renal replacement therapy. Exclusion criteria included patients admitted to the ICU post cardiac surgery, post liver transplantation, or for burns treatment.

The new follow-up study¹ specifically reports outcomes among patients with severe sepsis. Of 1,218 severe sepsis patients, 603 and 615 were assigned to receive albumin and saline, respectively. The study demonstrated a trend towards a mortality benefit in the unadjusted albumin-treated group (relative risk 0.87; 95% confidence interval 0.74–1.02; $p=0.09$). No difference in the renal or total Sequential Organ Failure Assessment (SOFA) score was seen among the two groups; 113/603 (18.7%) of patients assigned albumin were treated with renal replacement therapy compared to 112/615 (18.2%) assigned saline ($p=0.98$). Additionally, there was no significant difference between groups in the mean number of days in the ICU, mean number of days in hospital, mean number of days on renal replacement therapy and mean number of days on mechanical ventilation. However, patients allocated to saline received significantly higher volumes of the study fluid for the first three days; the ratio

of volume of saline to albumin administered on days 1–3 was 1.4:1.

The new analysis also examines a subset from the severe sepsis cohort, who had complete baseline data; 919/1,218 (75.5%). Variables with missing baseline data included various SOFA scores, serum albumin concentration, heart rate, ventilation status, central venous pressure and mean arterial pressure. In most cases, data were missing because a parameter or laboratory value had not been measured prior to the commencement of fluid resuscitation. Using a multivariate model, it was found that, when compared to saline, the use of albumin was independently associated with a decreased odds ratio for death at 28 days (adjusted odds ratio (OR), 0.71; 95% CI, 0.52–0.97).

In addition to an overall mortality benefit, the paper reports improvements in measures of intravascular volume support (heart rate and central venous pressure) with albumin compared to saline. The authors raise the possibility that "... on a population basis, small differences in intravascular volume status might give rise to significant differences in mortality."¹ Furthermore, the authors note that, in contrast to studies of other fluids used in resuscitation, no evidence of adverse renal function associated with albumin use compared to saline was detected.

Whilst these results provide indicative evidence that albumin may reduce mortality in patients with severe sepsis, further suitably powered studies are required to confirm this benefit and investigate the possible mechanisms. ■

References

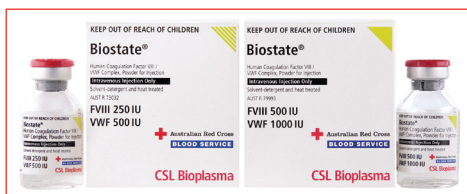
1. The SAFE study investigators. Impact of albumin compared to saline on organ function and mortality in patients with severe sepsis. *Intensive Care Med* 2011; 37(1): 86–96.
2. The SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350(22): 2247–56.

BIOSTATE® advisory statement

CSL Biotherapies has recently received reports of two patients with von Willebrand disease (VWD) being under-dosed with BIOSTATE due to a misunderstanding regarding the prescribing haematologist's dosing instructions. In both cases, the patient outcome was advised as satisfactory. However, to limit the possibility of similar future episodes, CSL Biotherapies, the Australian Haemophilia Centre Directors' Organisation (AHCDO), the Australian Haemophilia Nurses Group (AHNG), and the Blood Service have jointly prepared the following statement and recommendation:

"BIOSTATE contains two active entities – factor VIII (FVIII) and von Willebrand factor (VWF), in a 1:2 ratio. BIOSTATE is approved by the Therapeutic Goods Administration (TGA) for use in both haemophilia A (HA) and von Willebrand disease (VWD).

Upon receipt of TGA approval of BIOSTATE for the treatment of bleeding episodes in VWD (27 August 2008), CSL Biotherapies amended the BIOSTATE carton and vial to clearly state the content of both active entities (FVIII and VWF). This change was made to comply with the TGA's *Therapeutic Goods Order No. 69 – General requirements for labels and medicines (TGO 69)* which requires that the name(s) and quantity of all active ingredients contained in a prescription medicine should be displayed on the main label of the carton and *Best Practice Guidelines on Prescription Medicine Labelling (Nov 2005)* which states that the name(s) and strength(s) of the active ingredient(s) contained in a prescription medicine should be prominently and equally displayed on the carton."



Background to the two reports

Each involved a VWD patient presenting outside normal working hours:

- ❖ In the first case, the duty haematologist instructed '2,500 units of BIOSTATE'. Staff administered BIOSTATE – 2,500 IU of VWF (ie 1,250 IU of FVIII), whereas the haematologist had intended BIOSTATE – 2,500 IU of FVIII.
- ❖ In the second case, the duty haematologist instructed '8,000 units of BIOSTATE'. Staff administered BIOSTATE – 8,000 IU of VWF (ie 4,000 IU of FVIII), whereas the haematologist had intended BIOSTATE – 8,000 IU of FVIII.

Recommendation

CSL Biotherapies has discussed these two cases with AHCDO, the AHNG, and the

Blood Service, and all parties have agreed on the following recommendation:

- ❖ That all centres that stock or administer BIOSTATE should consider amending:
 - Clinical Practice Guidelines used by haematologists and in haemophilia treatment centres; and
 - Dispensing protocols for BIOSTATE used in Blood Banks and/or Pharmacies

such that both documents clearly state the following information:

- ❖ BIOSTATE contains both FVIII and VWF in a 1:2 ratio, and is approved for use in both haemophilia A and von Willebrand disease;
- ❖ Each order for BIOSTATE should specify the 'active entity' of the ordered dose. Examples: "BIOSTATE – 1000 IU of VWF" "BIOSTATE – 1500 IU of FVIII"; and
- ❖ Any order for BIOSTATE that does not specify the 'active entity' of the ordered dose should be clarified before the order is processed.

BIOSTATE PRESENTATIONS	WFI ² VOLUME	FINAL CONCENTRATION ¹		COLOUR WEDGE ON CARTON AND LABEL		
		FVIII	VWF	CURRENT	FUTURE ³	ITEM NO.
TGA APPROVED AND CURRENTLY SUPPLIED						
BIOSTATE 250 IU FVIII/500 IU VWF	5mL	50 IU/mL	100 IU/mL			33000185
BIOSTATE 500 IU FVIII/1,000 IU VWF	10mL	50 IU/mL	100 IU/mL			33000192
TGA APPROVED AND NOT YET SUPPLIED						
BIOSTATE 1,000 IU FVIII/2,000 IU VWF ⁴	10mL	100 IU/mL	200 IU/mL			NA

1. Nominal.
2. WFI = Water for injection
3. The colour wedge on BIOSTATE 250 IU FVIII/500 IU VWF will be changed to assist visual differentiation. Advice will be circulated at the time of change.
4. TGA approval 5 February 2009 – supply awaiting outcome of NBA Schedule 4 funding submission.

TU11

iTRANSFUSE
TRANSFUSION UPDATE 2011
 11–13 MAY NATIONAL WINE CENTRE ADELAIDE

VISIT transfusion.com.au for REGULAR TU11 UPDATES

Updated residual risk estimates for transfusion-transmitted infections

Blood Service estimates of the residual risks of transfusion-transmitted viral infections are based on published models and represent the median risk estimate derived using three models. These estimates are updated annually. As the order of magnitude of these risks is very small, the calculated median risk estimate may fluctuate from year-to-year.

For ease of interpretation, the Blood Service reports residual risks estimates which are lower than 1 in 1 million as “less than 1 in 1 million” rather than as the calculated median risk estimate. The rationale for this is that, when compared to everyday risks, any risk which is less than 1 in 1 million is considered to be “negligible”. The Blood Service will, however, provide the calculated median risk estimates upon request.

The viral risk estimates presented in Table 1 have been revised based on Blood Service data from 1 January 2008 to 31 December 2009 and the implementation of nucleic acid testing (NAT) for hepatitis B virus (HBV) during 2010.

There have been no reported cases of transmission by transfusion of classical Creutzfeldt-Jakob Disease (cCJD) and retrospective studies suggest that the possibility of such transmission of cCJD is remote.¹

To date, there have been no reported cases of vCJD in Australia. In the UK, there have been a small number of reported cases of putative transfusion transmission since 2004. In Australia, as a precaution, people who have spent a cumulative period of six months in the UK between 1 January 1980 and 31 December 1996 and/or had a transfusion in the UK between 1 January 1980 and the present time are not accepted as blood donors.

When considering the significance of specific risks, it is often useful to compare them to the risks associated with everyday living. The risk estimates listed opposite are very small when compared to everyday risks (refer to the Calman scale in Table 2 opposite). The chance of dying in a road accident, for example, is about 1 in 10,000 per year.

Reference

1. Dorsey et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. *Transfusion* 2009; 49: 977–984.

Table 1 Residual risk estimates for transfusion-transmitted infections

Agent and testing standard	Window Period (Days)	Estimate of residual risk 'per unit' ^a
HIV (antibody + NAT)	5.6	Less than 1 in 1 million
HCV (antibody + NAT)	3.1	Less than 1 in 1 million
HBV (HBsAg + NAT)	23.9	Less than 1 in 1 million
HTLV I & II (antibody)	51	Less than 1 in 1 million
Variant Creutzfeldt-Jakob Disease (vCJD) [No testing]		Possible. Not yet reported in Australia. See section to the left.
Malaria (antibody)	7–14	Less than 1 in 1 million

a. HIV, HCV, HBV risk estimates are based on ARCBS data from 1 January 2008 to 31 December 2009. HTLV risk estimate based on data from 1 January 2004 to 31 December 2009. For other agents refer below.

Viral estimates: Seed CR, Kiely P and Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotropic virus. *Intern Med J* 2005; 35(10): 592–8.

Malaria: Seed CR, Kee G, Wong T, Law M, Ismay S. Assessing the safety and efficacy of a test-based, targeted donor screening strategy to minimize transfusion transmitted malaria. *Vox Sang* 2010; 98(3 Pt 1): e182–92.

Table 2 The CALMAN Chart (Calman 1996^b) for explaining risk (UK risk per one year)

Negligible:	< 1,000,000 e.g. death from a lightning strike
Minimal:	1:100,000 – 1:1,000,000 e.g. death from a train accident
Very low:	1:10,000 – 1:100,000 e.g. death from an accident at work
Low:	1:1000 – 1:10,000 e.g. death from a road accident
Moderate:	1:100 – 1: 1000 e.g. death from smoking 10 cigarettes per day
High:	> 1:100 e.g. transmission of chickenpox to susceptible household contacts

b. Calman K. Cancer: science and society and the communication of risk. *BMJ* 1996; 313: 801.

Non-viral serious risks of blood transfusion

The most frequently reported serious or fatal complications of blood transfusion are bacterial contamination, transfusion-related acute lung injury (TRALI) and ABO incompatibility (the

latter mostly due to preventable patient or sample identification errors). Other serious risks associated with transfusion, based on overseas estimates, are outlined in Table 3.

Table 3 Reported non-viral serious risks of blood transfusion

Adverse reaction	Risk per unit transfused (unless specified)
Bacterial sepsis* – Platelets – Red cells	At least 1: 75,000 At least 1: 500,000
Haemolytic reactions – Acute – Delayed	1: 12,000 to 77,000 1: 2,500 to 11,000
Anaphylaxis – IgA deficiency	1: 20,000 to 50,000
Fluid overload/cardiac failure	Up to 1:100 per transfused patient
Transfusion-related acute lung injury	1: 5,000 to 190,000
Transfusion-associated graft versus host disease	Rare

* Clinically apparent reactions

Source: Blood Service clinical website (www.transfusion.com.au/adverse_events/adverse-reactions-blood)

medilink is published by Transfusion Medicine Services at the Australian Red Cross Blood Service to update health professionals with the latest news and research relating to transfusion. It is published in tandem with our electronic newsletter, *iTransfuse Express*, which is distributed in the months between issues of *Medilink*. If you or your colleagues would like to be added to either of these mailing lists, please email details to [Lisa Reid I Reid@redcrossblood.org.au](mailto:Lisa.Reid@redcrossblood.org.au). An archive of *Medilink*, *Med e-News* and *iTransfuse Express* can be accessed at www.transfusion.com.au. *Medilink* is printed with vegetable-based inks on 55% recycled and 45% elemental chlorine-free (ECF) sustainable plantation fibre.

Australian governments fully fund Red Cross for the provision of blood products and services to the Australian community.