



Armadale Health Service

RENAL NURSE PRACTITIONER CLINICAL PROTOCOL

**TITLE:**

MANAGEMENT OF RENAL ANAEMIA IN STAGE 4/5 CHRONIC KIDNEY DISEASE (Version 2)

This Clinical Protocol is devised for an exclusive use by the Renal Nurse Practitioner, Armadale Health Service.

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**MANAGEMENT OF RENAL ANAEMIA IN STAGE 4/5 CHRONIC KIDNEY DISEASE (Version 2)**

**ANAEMIA IN STAGE 4/5 CHRONIC KIDNEY DISEASE (Version 2)**



The Management of Renal Anaemia in Stage 4/5 Chronic Kidney Disease (Version 2 ) was revised by the authors, Casey Light and Dr. Hemant Kulkarni, who developed the original protocol in 2005. This updated version has been reviewed by the Clinical Protocol Development Review Panel consisting of representatives from pathology, pharmacy, and experts from the Armadale Health Service (AHS) Policy and Procedures Committee.

#### STATEMENT OF INTENT

Intent of the protocol "MANAGEMENT OF RENAL ANAEMIA IN STAGE 4/5 CHRONIC KIDNEY DISEASE (Version 2) " aims to:

- Define the Scope of Practice for a Registered Nurse Practitioner,
- Facilitate the Nurse Practitioner involvement in the management of renal anaemia
- Ensure availability of renal anaemia management for patients with chronic renal disease.

There by improving effectiveness, efficiency and quality of care in patients with renal failure.

This amended protocol aims to provide information updated for the available evidence in the management of "anaemia of CKD" in pre-dialysis and dialysis patients by the Renal Nurse Practitioner.

#### AGREEMENT

Armadale Health Service agrees to share this clinical protocol within the health care industry.

A copy of this protocol will be held at the Office of the Chief Nursing Office and will be made available online on the Department of Health's websites.



## INTRODUCTION

### Overview of condition

Anaemia in chronic kidney disease (CKD) remains one of the predictable and modifiable non-traditional cardiovascular risk factors (Foley, Parfrey, & Sarnak, 1998; Sarnak et al., 2003; Silverberg, Iania, Wexler, & Blum, 2004). Presence of anaemia is an independent risk factor for cardiovascular events and, in most cases, amplifies existing CVD risks (Silverberg, Wexler, Blum, Schwartz & Iania, 2004).

It is often present in moderate renal failure (GFR<60ml/min/1.73m<sup>2</sup>) (Kazmi, Kausz, & Khan, 2001) and becomes a clinical problem in the majority of patients in Stage 4 CKD (ie GFR <30 ml/min) (Appendix 1, Stages of CKD ).

Reported prevalence of anaemia in CKD is as below:

- Early Stage 4 CKD (GFR 25-34 ml/min/1.73m<sup>2</sup>): 51% (UK CKD guidelines, 2005).
- Late Stage 4/Stage 5 CKD (GFR <25 ml/min/1.73m<sup>2</sup>): 87% (UK CKD guidelines, 2005).
- Stage 5 CKD patients: ~ 60-80% (Hsu, McCulloch, & Curhan, 2002; Strippoli, Manno, & Schena, 2003).

Anaemia is associated with angina, left ventricular hypertrophy (LVH), left ventricular systolic dysfunction (Levin, Singer & Thomson, Ross, & Lewis, 1996), increased morbidity and mortality (Locatelli, Conte, & Marcelli, 1998), increased frequency and duration of hospitalisation, and mortality in haemodialysis patients (Gregory, Sarnak, Kostam, Pereira, & Salem, 2003).

Risk of cardiovascular disease (CVD) and anaemia of CKD increases commensurate with decline in GFR below 60ml/min (Sarnak et al, 2003).

Management of anaemia in CKD is important in reducing cardiovascular complications associated with anaemia and CKD. Anaemia in CKD patients is implicated in clinical symptoms such as fatigue, depression, reduced exercise tolerance, neuro-cognitive dysfunction, impaired immune responses and shortness of breath thus affecting overall quality of life (Levin, Thompson, & Ethier, 1999; Sarnak et al., 2003).

Development of recombinant Erythropoietin (EPO) and newer intravenous iron preparations have facilitated the successful management of renal anaemia with virtual elimination of blood transfusions. (Levin et al., 1999; National Kidney Foundation K/DOQI, 2001; Sarnak et al., 2003).

Correction of anaemia with erythropoietin therapy is associated with regression of LVH, delays progression of kidney disease, improves survival (Locatelli et al., 1998), lower rates of hospitalisation and reduced treatment costs especially in stage 4 CKD patients (Portales, Torralbo, & Martin, 1997).

Aggressive management with increasing use of ESA's in anaemia of CKD often led to worse outcomes.

Attempts to normalise Hb by ESA therapy is reported to increase mortality and morbidity since 2006. In 2006, CREATE (Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin) and CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) finally burst the high-hemoglobin bubble. These 2 large randomized trials (Drueke, T., Locatelli, F., Clyne, N., Eckardt, K and Macdougall, 2006; Singh, A., Szczech, L., Tang et al., 2006) that enrolled patients with stage 3 to 4 CKD found either no benefit or potential harm associated with targeting normal hemoglobin levels versus levels of 105 to 115 g/L. Concurrently, trials in patients with cancer were consistently finding increased mortality associated with ESA use (albeit at far higher doses than those used in CKD) (Bohlius, J., Schmidlin K., Brillant, C., et al, 2009). **These trails have changed the previous practice of increased ESA use and high target Hb.**

Hepatic Iron overload was noted in our cohort of hemodialysis patients (Kulkarni et al, (Abstract) ANZSN, 2008 ), leading to reduced iron dosing and thus reducing cumulative iron load.

Management of "anaemia of CKD" involves multifaceted investigations, follow up and treatment plans, that are elucidated in this revised version of the original protocol. This amended clinical protocol provides updated management guidelines for intravenous iron therapy and EPO in patients with Stage 4/5 CKD.



**Aetiology of “Anaemia of CKD”:**

Anaemia of CKD is usually normocytic and normochromic and is associated with EPO deficiency and shortening of red blood cell (RBC) survival. EPO production is markedly decreased in CKD, and RBC production as quantitated with ferrokinetics is subnormal; despite serum EPO levels remaining within the “normal” range. Excessive cytokine production in CKD (eg: IL-6, TNF $\alpha$ ) also leads to inadequate EPO production, interferes with EPO activity in bone marrow and inhibits the release of iron stores from reticuloendothelial system (Silverberg, Iania, Wexler, & Blum, 2001; Cooper, Mikhail, Lethbridge, Kemeny, & Macdougall, 2003).

**Definition of Anaemia of CKD**

Anaemia of CKD is defined as:

1. Hb levels less than <135g/L in males & <120 g/L in females, (K DOQI , 2006) AND
2. Established CKD (eGFR <30 or <45 ml/min/1.73m<sup>2</sup> in diabetics) (EBPG ) AND
3. Alternative causes anaemia as blood loss, Iron/ folate/Vitamin B12 deficiency are excluded

**Management Principles of anemia management in CKD:**

Current strategies for anemia management in CKD crudely attempt to mimic precise feedback mechanisms. Endogenous release of erythropoietin in response to anemia prevents apoptosis of early bone-marrow erythrocyte progenitors and permits proliferation, maturation, and increased output of erythrocytes, whereas erythropoietin suppression and subsequent increased apoptosis in erythroid progenitors occur in settings of higher erythrocyte mass. Because endogenous erythropoietin levels are often higher in persons with CKD than in control participants, most anemia in CKD must be multifactorial, with either concurrent bone marrow resistance to erythropoietin (often due to iron deficiency and inflammation) or increased erythrocyte destruction or loss contributing to anemia.

**Haemoglobin target for “Anaemia of CKD” (Including recent evidence):**

Haemoglobin target:

- Predialysis ESA naïve: Hb > 120 g/L (attempt to normalise)
- Predialysis and dialysis patients requiring ESA: 100- 120 g/L (aiming Hb levels between 105-115 g/L)
- Dialysis patients ESA naïve: >100 g/L
- ESA naïve **Hb target: 100- 120 g/L with aim to maintain Hb levels between 105 – 110 g/L**

**\* Targeting Hb levels above 130 g/L in pre-dialysis or dialysis patients is currently inadvisable. (Level 1 evidence) (CARI, 2008)**

*Haemoglobin concentrations above 130 g/L have been associated with an increased mortality in chronic kidney disease (CKD) patients (dialysis and pre-dialysis) and is therefore currently considered inadvisable. (Level I evidence) (CARI -Haemoglobin, 2008).*

Considering the newer evidence showing lack of evidence of high Hb (above 130) with increased adverse events on high dose EPO, day to day fluctuations in Hb levels, RPBS criteria for EPO prescription and lack of strong evidence to maintain Hb levels with defined ranges, we changed the policy of aiming Hb within wider range of 100 -120 g/L, targeting to maintain levels between 100 – 110 g/L. This will reduce interventions and frequent dose variations, considering associated clinical issues and greater autonomy to the Nurse Practitioner management.

Considering striking similarities in various national guidelines, we adopted to use Australian Guidelines (CARI) as standards for management of renal anaemia. We acknowledge that newer literature is not incorporated in these guidelines.

Appropriate changes to the protocol are thus done to incorporate latest evidence based on its strength and its impact on patient care.



## Summary of recent trials in “Anaemia of CKD”

In 2006, CREATE (Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin) and CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) finally burst the high-hemoglobin bubble. These 2 large randomized trials (Drueke,T., Locatelli,F., Clyne,N., Eckardt,K and Macdougall, 2006;Singh,A., Szczech,L., Tang et al.,2006) that enrolled patients with stage 3 to 4 CKD found either no benefit or potential harm associated with targeting normal hemoglobin levels versus levels of 105 to 115 g/L.

Concurrently, trials in patients with cancer were consistently finding increased mortality associated with ESA use (albeit at far higher doses than those used in CKD) (Bohlius, J., Schmidlin K., Brillant C., et al, 2009).

Of note, the largest ESA study to date (Pfeffer, M. 2008) continued, despite calls that it should be abandoned. Randomly assigning 4038 participants with stage 3 to 4 CKD, TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) compared hemoglobin normalization using darbepoetin with placebo, although salvage ESA could be given for hemoglobin levels below 90 g/L. Published in late 2009, TREAT (Pfeffer, M., Burdmann, E., Chen, C. et al. 2009) revealed no difference between randomization groups in the primary outcome, although an increased risk for stroke was associated with targeting normalization.

Given the emphasis of recent clinical trials on targeting high hemoglobin levels, critical knowledge gaps remain, most notably the absence of information evaluating lower hemoglobin targets (<125 g/L). The largest randomized, placebo-controlled outcome study to explore this range was the 1990 Canadian Erythropoietin Study Group (CESG) trial (Canadian Erythropoietin Study Group, 1990), which included 118 patients and lasted only 6 months. The placebo group in the CESG trial had a mean hemoglobin concentration of 74 g/L (SD, 12) as compared with 2 treatment groups that achieved mean hemoglobin levels of 102 g/L (SD, 10) and 117 g/L (SD, 17), respectively, by using 50% to 60% less epoetin than the normalization group in the Normal Hematocrit Trial. In the CESG trial, substantial benefits to quality of life and physical performance were associated with the 2 higher hemoglobin targets, although outcome measures did not differ between the 2 treatment groups. Subsequent larger clinical trials have not shown clinically meaningful sustained improvements in quality of life, although hemoglobin levels for the control groups in these studies were similar to the treatment groups of the CESG trial.

A second knowledge gap is the lack of data to facilitate individualization of therapies. Higher-functioning persons are probably more aware of the symptoms of anemia than more sedentary persons, thereby deriving greater benefit from higher hemoglobin targets (Prisant, A., 2010). A third gap, pertaining to the use of iron and other anemia-management agents, is the lack of data on concurrent administration of multiple anemia therapies.

A recent review (Palmer S et al, Annals of Int Medicine, May 4, 2010, 152 (9)) compiling 27 randomized trials of erythropoiesis-stimulating agents (ESAs) in patients with anaemia and chronic kidney disease from Jan 1966 to March 2010 showed:

- \* Treatment with ESAs that resulted in higher haemoglobin levels increased risks for stroke, worsening hypertension, and vascular access thrombosis more than strategies that resulted in lower haemoglobin levels (placebo, no treatment, or lower ESA dose).
- \* Effects on all-cause mortality, cardiovascular events, and quality of life were unclear.
- \* Underlying mechanisms for harms were not established.
- \* Therapy with ESAs that targets high haemoglobin levels is harmful for patients with chronic kidney disease.

\* Sub analysis of CHOIR data showed that the use of higher dose of ESAs rather than just high Hb values was associated with higher mortality. It is thus likely the patients needing high dose of ESAs are sicker and/ or have acquired EPO resistance.



## Anaemia Management for Haemodialysis patients at AHS

### Established protocols at Armadale Dialysis Unit:

- Regular investigations for anaemia and CKD complications are performed as per Appendix 5 which include FBP, Iron studies, Vitamin B12/ folate, and PTH.
- All patients receive Vitamin B complex/ Folic acid supplements following haemodialysis.
- ESA's are administered subcutaneously as per the Renal NP Protocol (Appendix 5), unless contraindicated.
- Parenteral Iron is administered on dialysis as per the established protocol (Appendix 4)
- Non-responsiveness to the therapy is investigated as per protocol (Appendix 3)
- Investigations are reviewed on monthly basis in a joint meeting involving Renal Physician, Renal Nurse Practitioner and Clinical Nurse Specialist (CNS) – Dialysis Unit.
- Renal Physician is responsible for supervision and management of Anaemia of CKD, including those which fall outside the parameters of NP, and is contacted for complex management issues.

### Target Parameters:

Hb target: 100- 120 g/L with aim to maintain Hb levels between 105 – 115 g/L

T Saturations: 20-40%

Ferritin: 200- 500 ng/L

### Exceptions:

Patient's nephrologists are permitted to provide targets outside this protocol, depending on the patient needs.

### Associated Roles

- Nurse Practitioner works in close conjunction with the CNS of the Dialysis Unit for management of anaemia and other dialysis related issues.
- Evaluation and management of other CKD related conditions in an individual patient are taken into consideration during the review at all times.
- Nurse Practitioner maintains her role in patient and staff education.
- Clinical decisions of Nurse Practitioner are followed by the dialysis staff, and discussed during the monthly meetings, if necessary.



**Patient Eligibility:**

- Late Stage 3 (eGFR <45 ml/Min/1.73m<sup>2</sup>), Stage 4 and Stage 5 CKD (inc patients on peritoneal dialysis)
- Established Anaemia (Hb <120 g/L) and/ or Iron Deficiency (TSAT <20%)
- Exclusion of alternative diagnosis for anaemia than CKD

**Source of Referral to NP Clinic:**

- Inpatients and outpatients at AHS
- Referral from Renal Physicians and other Renal Clinics
- Referral to NP Clinic from GP and other sources

**Evaluation:**

- Establish and confirm the presence of anaemia and its possible cause on history, physical examination and prevalent investigations
- Exclude haematinic deficiency (Iron Studies, Vitamin B12, Folate studies),
- If no cause is established: Exclude haemolysis (Reticulocytes counts, LDH, Haptoglobin), hyperparathyroidism and occult losses (Faecal Occult Blood x 3)
- If no cause is established or any significant positive finding on the investigations: Inform or refer to the Renal or Referring Physician
- EPO therapy is commenced in conjunction with Renal Physicians, and monitored as per protocol (Appendix 5.)

**Target Parameters:**

No parameters for iron studies are established in absence of anaemia

**Hb target:**

- Predialysis ESA naïve patients : Hb> 120 g/L (attempt to normalise)
- Predialysis and dialysis patients requiring ESA: 100- 120 g/L (aiming Hb levels between 105-115 g/L)

**Exceptions:**

Patient's nephrologists/ physicians are permitted to provide targets outside this protocol, depending on the patient needs.

**Associated Roles:**

- Nurse Practitioner works in close conjunction with anaemia coordinators and Same Day Unit for organising Iron therapy, EPO therapy
- Evaluation and management of other CKD related conditions (including Hep B vaccination) in an individual patient are taken into consideration during the review at all times.
- Nurse Practitioner maintains her role in patient and staff education.
- Clinical issues are discussed during the monthly meetings, if necessary.

## ROLE OF IRON METABOLISM in the MANAGEMENT OF ANAEMIA

Iron deficiency (**absolute or functional**) is common in CKD patients, with limited intake / absorption via the enteral route, blood loss due to collections and procedures, and comorbid inflammatory disease aggravating the blood loss.

Iron is an essential element needed for transport of oxygen required for production and survival of all cells in the human body. The human body tightly regulate iron absorption and recycling. However, there are no substantial physiological regulatory mechanisms for excreting iron. Iron homeostasis is thus dependent on feedback between body iron needs and intestinal iron absorption.

Iron absorption occurs mainly in the duodenum by enterocytes of the duodenal lining. Dietary iron is absorbed as heme protein or in its ferrous  $Fe^{2+}$  form. A duodenal ferric reductase enzyme (Dcytb) on the enterocyte brush border reduces ferric  $Fe^{3+}$  to  $Fe^{2+}$ . A protein called divalent metal transporter 1 (DMT1) then transports the ferrous iron across the enterocyte's apical membrane and into the cell.

Iron absorption is influenced by these factors acting simultaneously or inter-relatedly with body iron stores, erythropoietic activity, presence of anaemia or hypoxemia and presence of inflammation.

Iron taken up by the enterocyte is stored as ferritin, the largest amount of ferritin-bound iron is found in the liver hepatocytes, the bone marrow and the spleen. The liver's stores of ferritin are the primary physiological source of reserve iron in the body. Macrophages of the reticuloendothelial system store iron as part of the process of breaking down and processing haemoglobin from engulfed red blood cells.

Iron is also stored as a pigment called hemosiderin in a pathological process such as the result of cell damage or among people with iron overload due to frequent blood cell destruction and transfusions.

Iron is transferred out of the enterocytes by the basolateral transporter ferroportin. Iron released into the circulation binds to transferrin and is transported to sites of use and storage.

**Hepcidin has emerged as major iron regulator** since its discovery in 2001 and plays an integrated role in the absorption and movement of iron in the body by preventing gastrointestinal iron absorption and inhibiting iron release from macrophages and hepatocytes. Hepcidin is a 25-amino-acid peptide produced in the liver and influences systemic iron status by:

- decreases basolateral iron transfer in enterocytes thus reduces dietary iron absorption
- decreases functional ferroportin activity by rapid internalisation and degradation thus reduces iron export
- decreased iron export from reticuloendothelial macrophages and hepatocyte

Abnormality in hepcidin has implications in two clinical conditions: hereditary hemochromatosis and Anaemia of inflammation

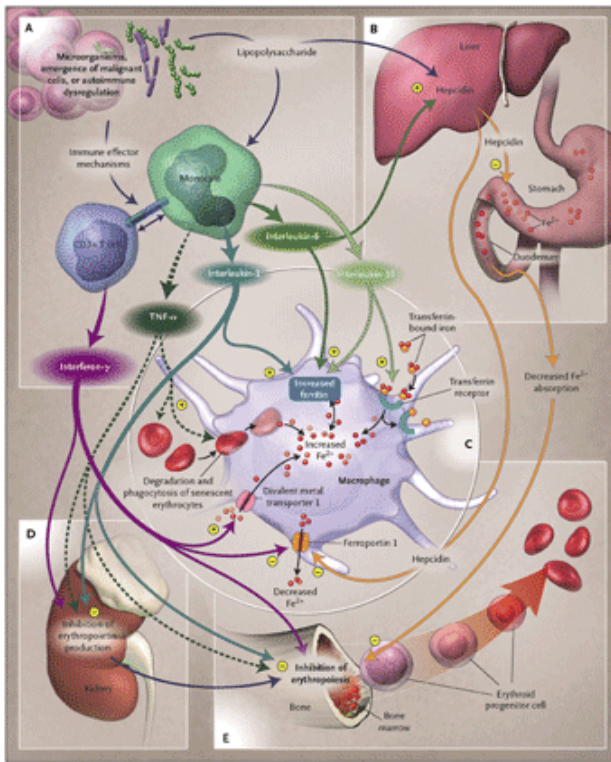
Increase red blood cells production decreases hepcidin production, thus increasing iron absorption and movement of iron in the body. Hence a low iron level will decrease liver production of hepcidin in order to enhance intestinal absorption of iron and vice versa.

On the other hand, high hepcidin level can lead to iron deficiency as a result of decrease iron absorption and the inhibitory movement of stored iron by degrading ferroportin in macrophages and hepatocytes. Hepcidin levels is increased in chronic inflammatory conditions ( counteracting signal to decreased hepcidin during accelerated erythropoiesis) may reduce iron movement and act like an emergency brake on RBC production , this may lead to patients requiring larger doses of ESA or render them as ESA unresponsive.

Indirectly, hepcidin may be an important factor in determining if patients will respond to ESA administration.

(Fleming, R & Bacon, B. 2005)





Source: Orchestration of Iron Homeostasis (Fleming, R & Bacon, B. 2005)

Iron-deficiency occurs when iron stores are inadequate for normal blood formation, and the requirements exceed the supply. There are two forms of iron deficiency in CKD patients: absolute and functional iron deficiency.

#### **Absolute iron deficiency**

Absolute iron deficiency occurs when there is no/insufficient iron available for the hemoglobin production. These insufficiencies may be due to multiple procedural, disease- and diet-related factors. The total available iron stores are insufficient to cover overall demand. NKF DOQI (2006) guidelines define absolute iron deficiency in CKD patients as ferritin values <200 ng/mL (haemodialysis) or <100 ng/mL (non-dialysis or peritoneal dialysis), with TSAT <20%.

#### **Functional iron deficiency**

Functional iron deficiency is, a failure to release iron rapidly enough to meet the bone marrow demand for RBC production, despite adequate body iron stores.

Functional iron deficiency is the most common cause of a poor response to ESA therapy (NKF K/DOQI, 2001; CARI, 2003; Level B evidence).. Functional iron deficiency has the following characteristics: Inadequate Hb response to ESA , serum ferritin normal or raised and Transferrin saturation (TSAT) <20 % . The NKF DOQI guidelines (2006) define functional iron deficiency in CKD patients as ferritin values >100ng/mL (>200 ng/mL for haemodialysis), with a TSAT <20%

#### **Evaluation of Iron Deficiency:**

Non-availability of suitable markers for functional and absolute deficiency in CKD patients at this time makes it essential to use multiple serum markers within a given clinical situation to decide regarding the use of iron supplementation.

TSAT and the serum ferritin are currently the two preferred tests for iron status (Evidence level I, NKF K/DOQI, 2001).

- TSAT (serum iron X 100 and divided by TIBC) reflects iron available for erythropoiesis.
- Serum ferritin reflects storage iron.

However, there is poor correlation of these parameters with Iron overload in dialysis population. (CONVENTIONAL SERUM IRON MARKERS DO NOT PREDICT LIVER IRON CONCENTRATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE Paolo Ferrari<sup>1,4</sup>, Hemant Kulkarni<sup>1</sup>, Shyam Dheda<sup>4</sup>, Susanne Betti<sup>1</sup>, <sup>2</sup>Colin Harrison<sup>2</sup>, John K. Olynyk<sup>3,4,5</sup> - IN PRESS)

Other parameters described in literature with varying sensitivities and specificities include:

- a) Percentage hypochromic RBCs (Low Mean Corpuscular Hb Concentration –MCHC)
- b) Soluble transferrin receptor levels
- c) Bone marrow stainable iron (Semiquantitative marker and invasive)
- d) Hepatic Iron Content by Ferriscan (MR Spectroscopy)

#### **Monitoring of serum iron parameters:**

##### Haemodialysis Patients:

Monitor Iron Studies 3 monthly as per protocol (Appendix 4)

##### Non Haemodialysis patients (Stage 4/5 CKD):

Monitor Iron Studies 3-6 monthly, more frequent if documented severe iron deficiency.

CARI guidelines recommend iron studies monitoring at 4 weeks following Initiation of EPO therapy whilst not receiving IV Iron, and 3 monthly during initiation of EPO therapy or while increasing the ESA dose, receiving Iron and following attainment of target Hb (CARI, 2003).



### **Treatment of Functional Iron Deficiency:**

NKF K/DOQI guidelines (2001) recommend additional IV iron (1-2 courses of 1 gm over 8-10 weeks) in haemodialysis patients who are on comparatively larger doses of ESA whose iron indices are within target ranges and whose Hb is below target. A response to either a first or a second course of IV iron (i.e., increase in Hb or decrease in ESA dose to maintain Hb) is followed by increasing the maintenance dose of iron supplementation. (NKF K/DOQI, 2001).

### **To overcome Functional Iron Deficiency this revised protocol advocates:**

- a) Target Iron parameters: TSAT >20% and Ferritin >200 ug/L (with normal CRP)
- b) 100mg IV Iron over 5 consecutive haemodialysis sessions in those suspected with functional iron deficiency.
- c) Assess response to IV iron and make necessary changes to ESA and IV Iron prescription.
- d) Investigate factors contributing to EPO resistance other than Iron and ESAs in conjunction with Renal Physician.



**Rationale:**

- Parenteral/Intravenous (IV) Iron Therapy is effective, convenient and safe therapy, for patients with CKD, who are usually on multiple oral medications; and is preferred modality at this unit for treatment of absolute or functional iron deficiency.
- Restoration of iron stores has been shown to correct anaemia (Besarab et al., 2000), reduce ESA dose requirements (Fishbane, Frei, & Maesaka, 1995; Besarab et al., 2000) and improves ESA responsiveness (NKF K/DOQI, 2001; Petroff, 2005).
- Nurse Practitioner has no role in oral Iron therapy, which can be pursued at primary care.

**Goals of parenteral (IV) Iron therapy:**

- Correct absolute or functional iron deficiency in order to achieve the target Haemoglobin, with minimum possible use of ESAs.
- Judicious use of therapy using the biochemical markers, despite knowing their limitations as markers of iron stores
- Avoid Iron overload with multiple aggressive iron infusions with regular monitoring.

**Caution with Intravenous (IV) Iron Infusions**

Multiple iron infusions may cause iron overload and is easily treated by withholding further infusions. IV Iron therapy is reportedly associated with increased risk of bacterial infections, reduced polymorphonuclear neutrophil function, and increase in oxidative stress and tissue iron deposition (Kletzmayer & Horl, 2002).

A Pilot study conducted at this unit involving nine hemodialysis patients with high ferritin showed significant hepatic iron overload, which correlated with duration of time on dialysis reflecting possibility of cumulative iron overload. This study did not find correlation of serum iron parameters, age, and sex with hepatic iron content. (Kulkarni H et al, ANZSN. 2008)

**This revised protocol recommends Withholding IV iron in patients with TSAT>40% and/or Ferritin >500 ug/L provided CRP is within normal limits** (See Appendix 4 –Protocol for IV Iron Management for Renal Nurse Practitioner).

**IV iron is withheld until next investigations in 3 months time. IV iron recommenced at half the previous maintenance dose after TSAT<40%, ferritin <500 ug/L and a normal CRP.** (CARI, 2003, Level B evidence)



## ERYTHROPOIETIN THERAPY

### Description of Erythropoietin (EPO)

Human EPO was isolated in 1976, its gene isolated and cloned in 1983 and recombinant human EPO (rHuEPO) became available for clinical use in the late 1980s.

Endogenous erythropoietin is a single-chain polypeptide hormone with a molecular weight of 30.4 kDa. Approximately 40% of the molecule is carbohydrate in the form of three N-linked glycosylation chain and one O-linked glycosylation chain. EPO gene is located on chromosome 7 and EPO is synthesized in the peritubular interstitial cells of the kidney in response to hypoxia. Normal range of plasma EPO is 4-30 mU/ml (Macdougall et al., 1999; Macdougall, 2000).

Recombinant human erythropoietin is manufactured by recombinant DNA technology with the Chinese hamster ovary cells as host cell (Macdougall et al., 1999; Macdougall, 2000).

There are now four forms of recombinant erythropoietin available in Australia:

1. Eprex™ (Epoetin alfa, *rch*)
2. Aranesp® (Darbepoetin alfa *rch*): Extra N-linked carbohydrate side-chain to the EPO molecule, claimed to prolong half-life than Epoetin alfa.
3. NeoRecormon (Epoetin Beta, *rch*): Epoetin Beta (highly purified glycoprotein) stimulates the proliferation and differentiation processes of the erythroid stem cell as well as the proliferation and maturation of the erythron. Hence lead to an increase in haemoglobin formation and an associated acceleration of cell maturation with reduction in the cell cycle time (MIMS 2008).
4. Mircera (PBS approved April 2010): (methoxy polyethylene glycol- epoetin beta) is a chemically synthesised ESA with a much longer half-life than erythropoietin. Mircera has a slower association to the EPO receptor and slightly faster dissociation, resulting in a lower affinity for the receptor and thus less receptor mediated endocytosis with reduced lysosomal degradation. Mircera thus has a longer half-life than erythropoietin which enables Mircera to be administered in a once monthly dosing regimen (UBM Medica, 2010).

For the ESA dosing refer Appendix 5: ESA Dosing Protocol for Pre-dialysis and Dialysis Patients



**DRUG FORMULARY for IRON**

Drug generic name	<b>FERROSIG® (Iron polymaltose)</b>
Poison schedule	S4
Therapeutic class	Iron supplement
Availability	2ml ampoule containing 318 mg iron polymaltose equivalent to 100 mg iron
Routes	Intravenous
Frequency administration	of Titrate to iron store levels (See flow chart, p 14)
Duration of order	Standing order following non complicated test dose
Action	Iron polymaltose is taken up by the reticuloendothelial system in the cell releasing Fe <sup>3+</sup> and polymaltose. The Fe <sup>3+</sup> is bound to transferrin and transported to the bone marrow and incorporated into haemoglobin
Indication for use	For iron supplementation or replacement
Contraindications for use	Hypersensitivity to iron polymaltose complex Iron overload Bronchial asthma Infectious renal complaints in acute phase
Side effects	Flushing, sweating, chills and fever Chest and back pain
Storage	Store below 25°C. Do not freeze. Protect from light

Source: FERROSIG® product information pamphlet, AMH (2008), MIMS (online)



**DRUG FORMULARY for Erythropoiesis Stimulating Agents (ESAs)**

There are now 4 ESAs available in Australia. Approved indications for authority are treatment of anaemia requiring transfusions, defined as a haemoglobin level of less than 100 g/L, where intrinsic renal disease, as assessed by a nephrologist, is the primary cause of anaemia

	<b>Darbepoetin alfa (rch)</b>	<b>Epoetin alfa(rch)</b>	<b>Epoetin beta (rch)</b>	<b>Methoxy polyethylene glycol-epoetin beta</b>
	<b>Aranesp</b> <b>Aranesp</b> <b>SureClick</b>	<b>Eprex</b>	<b>NeoRecormon</b>	<b>Mircera</b>
Production company	Amgen	Janssen-Cilag	Roche	Roche
Poison schedule	S4 (S100-Highly Specialised Drug Program)			
Description	Purified from genetic coded Chinese hamster ovary cell line Single chain with 165 amino acid proteins <b>MW 37,000 Daltons</b> Carbohydrate moiety contains 5 N-linked oligosaccharide chains. Provides longer serum half-life	Purified from genetic coded Chinese hamster ovary cell line <b>MW 30,400 Daltons</b> Protein moiety MW 18,244 Daltons Carbohydrate moiety has 3 N-linked and 1 O-linked COH gp	Purified from genetic coded Chinese hamster ovary cell line <b>MW 30,000 Daltons</b>	Continuous erythropoietin receptor activator
Availability	Pre filled syringes  10ug/ 0.4ml 60 ug/ 0.3ml 20ug/ 0.5ml 80 ug/ 0.4ml 30ug/ 0.3ml 100 ug/ 0.5ml 40ug/ 0.4ml 150 ug/ 0.3ml 50 ug/0.5ml  SureClick prefilled pens  20 ug / 0.5ml 80 ug / 0.4 ml 40 ug / 0.4 ml 100 ug / 0.5 ml 60 ug / 0.3 ml 150 ug / 0.3 ml	Pre filled syringes  1000 IU/ 0.5 ml 6000 IU/ 0.6ml 2000 IU/ 0.5ml 8000 IU/ 0.8ml 3000 IU/ 0.3ml 10000 IU/ 1.0ml 4000 IU/ 0.4ml 40000 IU/ 1.0ml 5000 IU/ 0.5ml	Pre filled syringes  1000 U/ 0.3 ml 2000 U/ 0.3 ml 3000 U / 0.3 ml 4000 U / 0.3 ml 5000 U / 0.3ml 6000 U/ 0.3 ml 10000 U / 0.6 ml 20000 U / 0.6 ml	Pre filled syringes  30 mcg / 0.3 mL (Turquoise) 50 mcg / 0.3 mL (Yellow) 75 mcg / 0.3 mL ( Red) 100mcg/ 0.3 mL (Aqua) 120mcg/ 0.3 mL (Lime) 200 mcg/ 0.3 mL (Purple) 360 mcg/ 0.6 mL (Salmon)
Mode of Administration	Subcutaneous or IV SureClick subcutaneous only	Subcutaneous or IV	Subcutaneous or IV	Subcutaneous or IV

**MANAGEMENT OF RENAL ANAEMIA IN STAGE 4/5 CHRONIC KIDNEY DISEASE (Version 2)**



Contraindications	Uncontrolled hypertension mammalian cells derived product sensitivity	Uncontrolled hypertension Known sensitivity to mammalian cells derived product Elective surgery with severe coronary , peripheral, carotid, cerebral vascular disease, recent MI, CVA unless autologous transfusion Patient who developed pure red cell aplasia following treatment	Uncontrolled hypertension, MI, stroke in preceding month, unstable angina, DVT risk, thromboembolism history.	Uncontrolled hypertension Hypersensitivity to the active substance or any of the excipients
Side effects	Flu like symptoms such as dizziness, drowsiness, fever, headache, muscle and joint pain and weakness Severe headaches Sudden tiredness or sudden short of breath Pure red cell aplasia	See adverse reactions		
Adverse reactions	Peripheral oedema. Hypertension, hypotension, headache, GI upset. Musculoskeletal symptoms. Fatigue, CV/thrombotic event including CVA, vascular access thrombosis, injection site pain, dyspnoea, cough, hypersensitivity reaction including urticaria , very rare: pure red cell aplasia	Hypertension, seizure, thrombotic/vascular events eg myocardial ischaemia, infarction, CVA, TIA, DVT, pulmonary emboli,, aneurysm, retinal, shunt thrombosis, thrombocytopenia, flu-like symptoms, bone pain, chills rash, urticaria, headache, arthralgia, injection site reaction, peripheral oedema, GI upset, pyrexia, Rare: Pure red cell aplasia	Increase risk CV, thrombotic events, hypertension, hypertensive encephalopathy, seizure, hyperkalemia, over hydration, coronary heart disease, URTI, UTI, asthenia, leucopenia, thrombocytopenia, antierythropoietin Ab mediated PRCA, menstrual disorder, inj site reaction, GI upset, headache, dizziness, hypersensitivity, flu like symptoms	Hypertension, headache, vascular access thrombosis, hypersensitivity, hot flush, maculopapular rash, hypertensive encephalopathy
Dosing	Initial 0.45 mcg/kg weekly	Initial 50 IU/kg three times a week Maximum Should not exceed 200 IU/kg three times a week	Initial 60 IU/kg weekly Maximum Should not exceed 720IU/kg weekly	Initial 0.6 ug/kg fortnightly



Storage	Store at 2°C to 8°C, do not freeze, do not shake Protect from light
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Source: CMP Medica 2008; UBM Medica 2010; MIMS (Online) <https://www.mimsonline-com-au>;  
Australian Prescriber, 2009; 32:165-171; AMH Section 7.5.1



## SCOPE OF THIS PROTOCOL

Adult patients with stage 3-5 CKD with established anaemia or on active treatment for anaemia of CKD

1. Are currently on **OR** need treatment with parenteral Iron and/or Erythropoietic agent for treatment of anaemia, **AND**
2. Folate or Vitamin B12 deficiency is treated **AND/OR**
3. Malignancies or active GI bleeding are excluded and treated **AND/OR**
4. Under-dialysis, hyperparathyroidism are investigated and treated **AND/OR**
5. Active inflammation or infection is investigated and treated with Renal Physician.

## EXPECTED OUTCOME OF THIS PROTOCOL

The major outcomes considered for this protocol are:

1. **To achieve and maintain haemoglobin targets**
2. **Improved treatment delivery**  
Early detection of correctable deficiencies of folate, Vitamin B12, iron deficiency  
Reduce use of ESA  
  
Diagnose contributory cause of anaemia
3. **A Nurse Practitioner-led renal anaemia management:** Assist Renal Physician/s in management of CKD complications, increased awareness amongst staff and patient. Involvement of NP in clinical care of the CKD patients provides improved continuity of care with more education.
4. **Promote consistency with guideline-based Iron and ESA therapies** in the unit.
5. **Auditing:** Protocol will be audited on yearly basis for shortcoming and updates with appropriate modifications.

Pre and post-protocol implementation assessment parameters include:

- Efficiency of protocol
- Establishing and auditing key performance clinical indicators (See *clinical performance and evaluation*, page 22)
- Patients' experience about the NP's role in renal anaemia management
- Nursing staff's experience regarding:
  - # The NP's role in renal anaemia management
  - # Compliance and user friendliness of the protocol
  - # Impact of the protocol on the renal nursing staff

The collection of data should occur immediately before the protocol implementation, follow by 6 and 12 months post protocol implementation.



## EVIDENCE BASE

This revised clinical protocol is developed after literature research and with references from:

- a) National and International best practise guidelines:
  - The CARI guidelines: Caring for Australians with Renal Impairment
  - NKF K/DOQI: National Kidney Foundation Kidney/ Dialysis Outcomes Quality Initiative guidelines
  - NICE: National Institute for Clinical Excellence
  - EBPG: The European Best Practice Guidelines
  - The UK CKD guidelines
  - National Guideline Clearinghouse (Online)
- b) ANZDATA (Australia and New Zealand Dialysis and Transplant Registry)
- c) Medline (OVID)
- d) Cochrane library (Online)
- e) PREMEDLINE (OVID)
- f) Synergy full text journals (Online)

Recommendations contained in this protocol are based on the level of evidence that measures relevant outcomes and demonstrates a strong, clinically important benefit effect of the intervention. The rating system to indicate the levels of evidence is as set out in the National Health and Medical Research council (NHMRC, 1999). CARI guidelines use a simpler form of evidence classification that is compatible with the National Health and Medical Research Council classification. The correlation between the two systems is indicated as below:

LEVEL	NHMRC classifications	CARI classifications
I.	Evidence obtained from a systemic review of all randomised controlled trials	A. Randomised controlled trials and Meta-analyses
II.	Evidence obtained from at least one properly designed randomised controlled trials	
III-1.	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)	
III-2.	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group	B. Descriptive studies
III-3.	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group	
IV.	Evidence obtained from case series, either post-test or pre-test and post-test	C. Consensus opinion



## REVIEW

The Nurse Practitioner will educate the dialysis nursing staff to comply with guidelines for the management of anaemia and will be responsible for reviewing results, adjusting iron and ESA doses, and/or ordering relevant investigations as per protocol.

Progress and response to the therapy should be documented in the patient's medical records and the treatment plan reviewed as necessary with the Renal Physician.

A prospective evaluation of this protocol should be conducted in first six months, with or without involving other dialysis units within the South Metro Area Renal Services to evaluate the efficacy of this protocol and carry out necessary modifications after an audit.

## IMPLEMENTATION PLAN

The implementation plan of the revised protocol includes:

- Staff education to update the changes in this revised version, promote staff awareness of reference sources , most recent relevant journal articles and scientific research outcomes to support changes made to this protocol
- The submission of this clinical protocol to the Department of Health (DOH) for approval in accordance with legislative requirements, after review by the Armadale Health Service Nursing Practice Committee and Management Advisory Committee.
- A schedule of quality activities to be performed, with yearly activity reporting to the AHS Medical Advisory Committee.
- The quarterly reporting of this protocol to the AHS Senior Executive Advisory Committee after its introduction and annually to DOH.
- The provision of effective clinical supervision by the Armadale Health Service to maintain the clinical competencies of Nurse Practitioners and regularly assess the risk management procedures related to the Nurse Practitioner's role.



## EVALUATION PLAN

A sound clinical governance framework is based on continually improving service quality and clinical excellence, ensuring accountability and safeguarding optimal health care standards. This framework ensures that the Nurse Practitioner delivers consumer focused, safe and quality health care that can be evaluated across the health service to provide dependable and quality outcomes for the patients.

In Western Australia, the model for clinical governance of nurse practitioner practice is based on four pillars (DOHWA, 2003):

1. Clinical performance and evaluation
2. Professional development and management
3. Clinical risk
4. Consumer value

The Armadale Health Service is committed to a systematic process to audit and evaluate the role of the Renal Nurse Practitioner in managing Renal Anaemia on an annual basis according to this framework that includes:

- Intended outcome
- Effectiveness
- Appropriateness
- Audit of utilisation and compliance of the protocol
- Accessibility and effectiveness of the protocol
- Consumer feedback
- Assessment of quality and safety

### 1. Clinical performance and evaluation

This current modified clinical protocol should be audited and reviewed after six months following its implementation and then at least every twelve months by the Nurse Practitioner and approved by the Nursing Practice Committee to ensure adherence of current best practice in the area.

Assessment parameters considered are:

	Pre NP intervention	6 months post NP intervention
<b>Targets</b>		
Hb g/L (Mean +/- 2 SD)		
Hb >100g/L (%)		
TSAT >20%		
% Hb <100 g/L and etiologies		
Hb response to IV Iron		
<b>Cost effectiveness:</b>		
ESA use (U/kg/wk)		
Hb/ESA weekly dose (ratio)		
Hb/weekly Fe dose (ratio)		
Change in Hb/ESA weekly dose in individual patient		
Iron use (mg/patient/wk)		
<b>Co-morbidities:</b>		
Blood transfusions		
Hospitalisation		
<b>Other CKD parameters (mean)</b>		
Albumin		
Vitamin D		
CRP		
PTH		



The Renal Nurse Practitioner will compile a database to monitor monthly laboratory investigations, dialysis adequacies, ESA and iron doses. The Renal Nurse Practitioner works in conjunction with Renal Physician in cases where patients are not achieving set targets.

This clinical protocol is disseminated to Clinical Protocol Development Review Panel for inputs in clinical, pharmacological, diagnostic, quality management, research and nursing practice components.

## **2. Professional development and management**

This process ensures that the nurse practitioner possesses skills and competencies required for the designated area of Renal Dialysis and maintains relevant professional standards. Indicators to measure effectiveness of the Renal Nurse Practitioner's role and improvement in patient outcomes using this clinical protocol will be established.

## **3. Clinical risk**

This process focuses on minimising risk and improvement in clinical safety by monitoring, recording and reporting clinical incidents and adverse events, conducting root cause analysis and developing risk management processes. The Australian Incident Monitoring System (AIMS) is employed at AHS for reporting unpredictable adverse events; qualitative and quantitative reports provide data for implementing safety and quality improvement strategies in order to improve patient outcomes.

## **4. Consumer value**

The Armadale Dialysis Unit strongly encourages involvement of the patients and their carers in renal replacement therapy by providing information on their condition and treatment regimes, supporting informed decision-making and ensures accessible and equitable health care to the patient and community. A continuous quality improvement process is in place for conducting patient satisfaction surveys on the ease of access, knowledge and understanding of the service provided by the Nurse Practitioner.



## DISCHARGE

### Criteria of discharge:

Patients are considered discharged when they are:

- Transferred permanently to another centre, transplanted or withdrawn from dialysis
- Unwilling to continue care for any reason
- No longer patients of Armadale Health Services including its dialysis unit

### Social support:

Social support provided to the patients includes:

- Education and information about medications including their adverse effects
- Information about storage and transport of EPO syringes
- Arranging supply of EPO prior to travel
- Supply of contact details for any problems

### Treatment plan:

The treatment plan provided to Medical Practitioner on patient's discharge include:

- Details of current EPO doses, last dose of IV Iron treatment (if applicable)
- Trend results of blood tests performed over the last 3 months
- Relevant clinical information: eg. Adverse events, diagnosis and latest clinic letter

### Consumer handout:

Consumer handouts provided prior to discharge or travel include:

- Education and information about medications including their adverse effects
- Information about storage and transport of EPO syringes
- Information about safe and proper disposal of used EPO syringes
- Contact details



**APPENDIX 1 : STAGES OF CKD**

**NKF K/DOQI: Classification of the Stages of CKD**

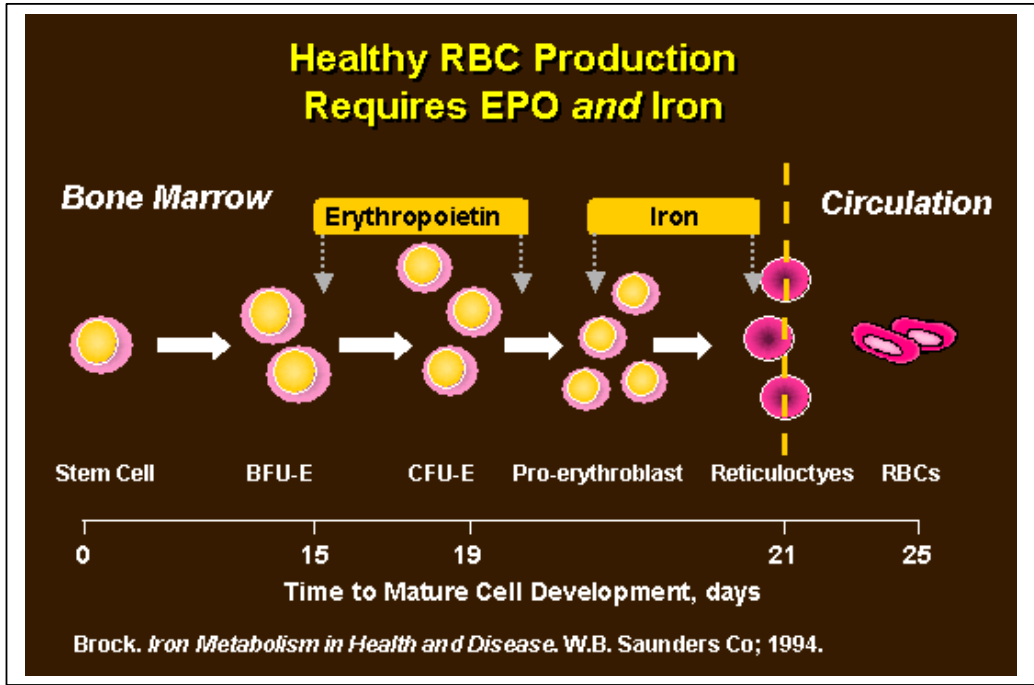
**Table 3. Chronic Kidney Disease: A Clinical Action Plan**

Stage	Description	GFR (mL/min/1.73m <sup>2</sup> )	Action*
	At increased risk	■90 (with CKD risk factors)	Screening CKD risk reduction
1.	Kidney damage with normal or ↑ GFR	■90	Diagnosis and treatment Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3.	Moderate ↓ GFR	30-59	Evaluating and treating complications
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5.	Kidney Failure	<15 (or dialysis)	Replacement (if uremia present)

Source : [http://www.kidney.org/professionals/doqi/kdoqi/p1\\_exec.htm](http://www.kidney.org/professionals/doqi/kdoqi/p1_exec.htm)



**APPENDIX 2: RBC PRODUCTION**



**Healthy RBC Production Requires EPO and Iron**

Epoetin (EPO) and iron function as independent erythropoietic factors. Epoetin acts in the bone marrow to stimulate the expansion of burst-forming units (BFU-E) and colony-forming units (CFU-E). Over 10 to 14 days, this will lead to increased red cell production. Iron stimulates erythropoiesis later in the red cell maturation cycle, at the pro-erythroblast stage (Brock, 1994).



**APPENDIX 3: CHECK LIST FOR CAUSES OF EPO HYPORESPONSIVENESS**

**Figure 3**  
**Triage Checklist for Ruling Out Inflammation/Infection and Causes of EPO Hyporesponse**

A. Serum ferritin is an acute-phase reactant and is elevated during inflammation and infection. Clinicians should look for acute exacerbations of the following common causes of inflammation and infection in hemodialysis patients:

Inflammation <sup>1</sup>	Infection <sup>1</sup>
Dialysis	Access site (catheter)
Diabetic skin ulcer	Urinary tract infection
Arthritis	Wound
Cellulitis	Abscessed teeth
Surgery	Pneumonia
Gout	Hepatitis B and C

**Patient-Specific Anemia Analysis Methodology**

- A. Patient presentation? What is different? What else could be causing inflammation? \_\_\_\_\_  
 B. Look at the last 3 quarterly/monthly TSAT and serum ferritin levels to assess a trend.

Date				
Serum Ferritin				
TSAT				

- C. When was IV iron last administered and how much? \_\_\_\_\_  
 K/DOQI recommends 1-3 g per year.<sup>2</sup> How much IV iron has the patient received in the last:  
 Month? \_\_\_\_\_ Quarter? \_\_\_\_\_ Year? \_\_\_\_\_  
Example: If serum ferritin is rising without IV iron, it is not likely a true measure of iron status. Has the patient gone 3 months without IV iron, yet serum ferritin is still elevated? If so, it is not likely due to iron overload.  
 D. **Functional Iron Deficiency?** Consult MD about administration of 1 g of IV iron over 8-10 weeks. If Hgb improves or EPO needs decrease, the patient probably had functional iron deficiency. If not, rule out other possible causes of infection and inflammation.<sup>2</sup>  
 E. **Rule out inflammation and infection.** Consult MD about ordering a CRP. CRP levels in hemodialysis patients are normally 10-20 mg/L (value for standard CRP); >20 mg/L usually indicates an inflammatory state.<sup>3,4</sup> A high CRP can affirm you should look for some underlying inflammation. Think of all potential causes of inflammation and try to resolve that condition.  
 F. **Some additional questions to consider when assessing anemic patients:**

Recent hospitalization or surgery? _____	Unreliable patient compliance and disclosure? Consider social worker consult or dietary consult _____
Catheter or any change in access? _____	Possible lab error? _____
GI bleed? Access bleeding? _____	Bone disease? _____
Low albumin, prealbumin, transferrin? _____	Aluminum toxicity? _____
Possible malnutrition? _____	Nonfunctioning arteriovenous grafts or rejected transplants? These can harbor undiagnosed infections/inflammation and decrease EPO efficacy <sup>5,6</sup> _____
Has patient been tested for HIV? _____	Is patient a smoker? Do they have undiagnosed asthma or emphysema or cancer? _____
Autoimmune diseases? _____	Check medication compliance for untreated underlying inflammatory conditions _____
Co-existing medical conditions? Inflammatory diseases exacerbated? _____	

CRP = C-reactive protein; EPO = recombinant human erythropoietin; Hgb = hemoglobin; K/DOQI = Kidney Disease Outcomes Quality Initiative; TSAT = transferrin saturation.

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Source: Bowe & Ammel, 2005, p. 6, Fig 3



## APPENDIX 4: RNP Protocol for IV Iron Management

### RNP Protocol for IV Iron Management

**Inclusion:** Absolute or Functional Iron Deficiency with anaemia of CKD (eGFR <60 ml/min/1.73m<sup>2</sup>)

**Exclusions:** Patients allergic to IV-Fe, pregnant women, active untreated infection, active arthritis, Hb >110g/L not on ESA's

#### Iron Studies Target in patients with Anaemia of CKD:

	TSAT (%)	Ferritin ug/L	CRP mg/L
Pre-dialysis and Peritoneal Dialysis	20%-40%	100-500	< 10
Haemodialysis	20%-40%	200-500	< 10

#### Non haemodialysis (Stage 4/5) and Peritoneal Dialysis patients:

Patients are admitted to Same Day Unit (SDU) for IV iron infusion after informing the indication, procedure, precautions and possible adverse effects.

Dose: 500-1500 mg of IV iron given as infusion (As per SDU Policy Manual, Armadale Hospital)

**Post IV Iron monitoring:** Full Blood Picture (FBP) (3-4 weeks following infusion), Iron studies (2-3 months following infusion)

**Report:** if any adverse events to infusion, or if >2 IV treatments are needed within 6 months.

#### Haemodialysis patients:

##### Initiation and maintenance dose

TSAT (%)	Ferritin (ug/L)	CRP (mg/L)	IV Iron dose
>40%	>500	<10	Withhold until TSAT <40% & Ferritin <500
< 20%	<500	<10	100 mg weekly
> 21% - 30%	<500	<10	100 mg fortnightly
>31% - <40%	<500	<10	100 mg monthly
Functional Iron deficiency* Hb < 100g/L			
<20%	>200	<10	100 mg x 5 dialysis sessions

\***Functional iron deficiency** is the delayed release of stored iron occurring in CRF, which reduces the response to erythropoietin.

#### Waiting time for Iron studies following Fe infusion (NKF K/DOQI guidelines)

IV Iron dose	Waiting time prior to blood testing
100-125 mg dose	None
200-500 mg dose	At least 7 days
1000 mg or more	At least 14 days



**Appendix 5: RNP Protocol for Erythropoietin Therapy**

**RNP Protocol for Erythropoietin Therapy**

**Pre-requisites:**

- 1) Satisfy **S-100** condition: Treatment of anaemia, defined as Hb <100 g/L, where an intrinsic renal disease, as assessed by a nephrologist, is the primary cause of anaemia.
- 2) **Iron replete:** TSAT >20% and S. Ferritin >200 ug/L;
- 3) Treated deficiencies for Vitamin B12, folate deficiency, and other causes of anaemia are reasonable excluded.

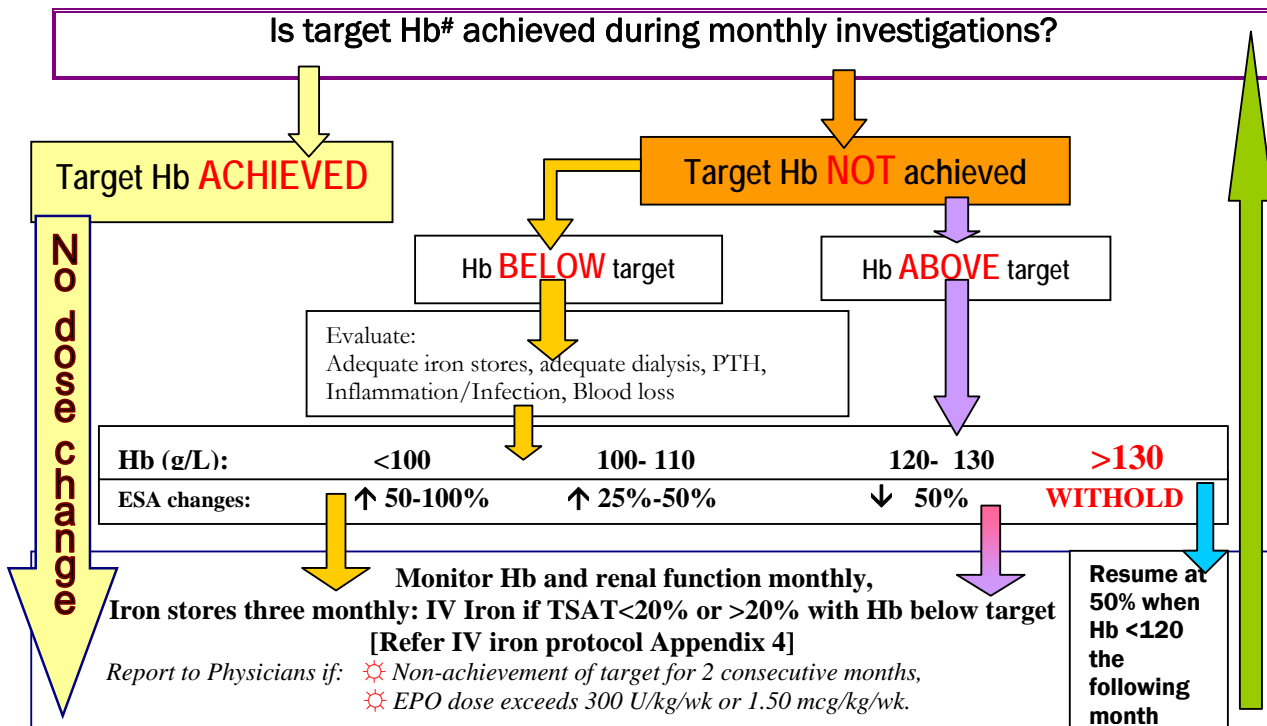
**Considerations during EPO therapy include:**

1. IV iron should be administered for patients on dialysis or those with documented iron deficiency (functional and absolute) (CARI, 2003; Level C evidence)
2. Check Hb 4-8 weeks following IV iron and/or EPO treatment until target is reached, and then 1 monthly (dialysis population) and 3 monthly (non dialysis population).
3. ESA dose increment should not occur more frequently than monthly (CARI, 2003; Level C evidence).
4. Hb rise should not exceed 10g/L per month (average over three months) (CARI, 2003; Level C evidence)

**Initiation dose**

Hb g/L	Epoetin alpha	Darbepoetin alpha	NeoRecormon	Mircera
<100 g/L	50 IU/kg 3 times a week	0.45 mcg/kg/wk	60 IU/kg/week	0.6 ug/kg/fortnight

**Maintenance Dose**



## GLOSSARY

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzymes inhibitors
AHS	Armada Health Service
ANZDATA	Australian and New Zealand dialysis and transplant registry
ATIIRB	Angiotensin II receptor blockers
BFU-E	Burst-forming units -E
CARI	Caring for Australians with Renal Impairment
CFU-E	Colony-forming units-E
CPP	Calcium X phosphate product
CCB	Calcium channel blockers
CKD	Chronic kidney disease
CRP	C-reactive protein
CSN	Canadian Society of Nephrology
CVD	Cardiovascular disease
DOH	Department of Health
EBPG	European Best Practice Guidelines
EPO	Erythropoietin
ESA	Erythropoietic stimulating agents
ESRD	End stage renal disease
ESRF	End stage renal failure
Fe	Iron
GFR	Glomerular filtration rate
GI	Gastrointestinal
Hct	Hematocrit
Hb	Haemoglobin
IV	Intravenous
LVH	Left ventricular hypertrophy
MCHC	Mean Corpuscular Haemoglobin Concentration
NHMRC	National Health and Medical Research Council
NKF K/DOQI	National Kidney Foundation Kidney/Disease Outcomes Initiatives
NP	Nurse Practitioner
PCR	Protein Catabolic Rate
PD	Peritoneal dialysis
PTH	Parathyroid hormone
QOL	Quality of life
RBC	Red blood cells
RCT	Randomised Controlled Trial
TIBC	Total iron binding capacity
TNF $\alpha$	Tumour necrosis factor alpha
TSAT	Transferrin saturation



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