Learning Package

Health
Hunter New England
Local Health District

Renal: Renal Anaemia

Sites where Learning package applies	Clinical areas where care is provided to patients with renal disease
Description	This learning package explores anaemia & its relationship with Chronic Kidney Disease (CKD) and End Stage Kidney Disease (ESKD) patients.
Target audience	Nephrology and Non-nephrology clinical staff who provide care to people with CKD and ESKD.
Learning Outcomes, On completion of this package you will be better able to:	• Understand the definition, signs & symptoms, classifications, cause and treatment of anaemia • Understand hypo-responsiveness to Erythropoietin Stimulating Agents (ESA) • Understand the role of iron replacement therapy in the treatment of anaemia associated with renal disease

Keywords	Renal; Anaemia; Dialysis; Chronic Kidney Disease
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Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- Infection Prevention and Control Policy [PD2017_013]
- NSW Health Policy PD 2005_406 Consent to Medical Treatment http://www.health.nsw.gov.au/policies/PD/2005/pdf/PD2005_406.pdf
- Renal Guidelines and Procedures http://ppg.hne.health.nsw.gov.au/

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Renal: Renal Anaemia

Learning Package

2018

NSW GOVERNMENT Health
Hunter New England
Local Health District

Learning Package Overview

Purpose: This learning package explores renal anaemia in relation to signs and symptoms, classifications and causes, along with treatment options most commonly associated with Chronic Kidney Disease (CKD). It also looks at hypo-responsiveness to Erythropoietin Stimulating Agents (ESA) and the role of iron replacement therapy.

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Introduction

This package is one of a suite of packages aimed at offering guided learning for nephrology nurses. The package aims to enhance theoretical knowledge leading to improved clinical practice as they care for patients with anaemia associated with Chronic Kidney Disease.

Disclaimer

This learning package has been prepared by health professionals employed in Hunter New England Local Health District in the Renal Services. While all care has been taken to ensure that the information is accurate at the time of development, the authors recommend that all information is thoroughly checked before use if utilised by another unit, context or organisation.

Naming Convention

Renal: Renal Anaemia

Aim

To enhance knowledge of Nephrology and Non-Nephrology clinical staff who provide care to patients who have Chronic Kidney Disease and associated Renal Anaemia.

Learning Outcomes or Learning Objectives

Completion of this learning package will enable the learner to:

- *Understand the definition, signs & symptoms, classifications, cause and treatment of anaemia.*
- *Understand hypo-responsiveness to Erythropoietin Stimulating Agents (ESA)*
- *Understand the role of iron replacement therapy in the treatment of anaemia associated with chronic disease.*

Pre-requisites

There are no formal prior learning requirements to undertake this package. However this forms part of the learning pathway for a nephrology nurse following completion of

- Haemodialysis or Peritoneal Dialysis SDLP
- Renal Anatomy and Physiology SDLP (This will assist your understanding of the impact of anaemia in the chronic kidney disease population.)

Learning Package Outline

The package is designed to be a self-directed learning experience that will guide you through the literature and clinical issues related to Renal Anaemia.

This package is developed within an adult learning framework so not all activities need to be documented but it is expected that you will complete them in order to facilitate your learning.

Problem based learning

This program is based on a problem-based approach to learning. This approach has been chosen to enhance critical thinking, and to create a body of knowledge that the learner can apply to practice.

Instructions for participants

- It is estimated it will take an average of 4 hours to complete this package.
- Completion of this package is equivalent to Continuing Professional Development (CPD) hours which is a requirement for National Registration. Evidence of CPD can be generated using the reflection on learning page at the end of the package.
- Self-directed learning will be required to complete this package. Some activities will include essential reading and others will have additional supplementary readings that participants can undertake to further consolidate their knowledge.
- A brief outline of the topic followed by recommended readings & learning activities that will reinforce key points guide participants study.
- There is a suggested reference list but it is by no means complete. Please read widely to facilitate your learning. Journal articles can be accessed through CIAP. The online readings are not provided within this document due to copyright law restrictions. If you have any difficulty locating the readings please seek assistance from your relevant NE/CNE/CNS/CNC or hospital library.

This SDLP uses the following icons:

	READING **This icon alerts you to undertake reading related to the topic, which may include Guidelines and Procedures, Journal Articles or Books**
	LEARNING ACTIVITY **This icon denotes a learning activity or competency assessment that you will need to complete**
	GUIDELINES **This icon alerts you to the presence of a guideline or procedure related to the subject**

Assessment process

When completed, you can return the package to relevant NE/ CNE/CNC/CNS who will discuss it with you.

Reflection tool

At the completion of the learning package there is a reflection form that will assist you in reflecting on the package and how it meets your professional development needs.

Evaluation

A Learning Package Evaluation form when you have completed this package is found on page 31. You will need to return this to the relevant CNE/NE/CNC/NP. This form is used to inform future updates and modifications of the learning package according to ongoing feedback from the user.

Overview of Anaemia

- *Understand the definition, signs & symptoms, classifications, cause and treatment of anaemia.*

Definition

Anaemia is defined as a reduction in the normal number of functional red blood cells (RBCs). This can be either:

- A decreased number of total circulating RBCs
- A normal number of RBCs which are, however abnormal in size, shape or haemoglobin (Hb) content.

According to the World Health Organisation, anaemia is defined in general population as haemoglobin levels <12.0 g/dL in women and < 13.0 g/dL in men (Schrier, S. 2017).

The 2011 Kidney Health Australia – Caring for Australasians with Renal Impairment guidelines recommend maintaining haemoglobin levels between 100 – 110 g/L for anaemic chronic kidney disease (CKD) patients (McMahon & MacGinley, 2011).

There is also a body of evidence to suggest that haemoglobin target levels between 100 and 115 g/L should be the aim for patients with CKD and definitely not levels above 130g/L which may be harmful (MacGinley & Walker, 2013).

It is also important to remember that anaemia is a laboratory finding and should not be considered a diagnosis in itself, but an indicator of a disease process, such as kidney injury, deficiency states, or malignancy. It is difficult to correct anaemia while underlying disease processes continue unchecked (Lerma, 2017).

READING

1. MacGinley, R and Walker, R. (2013) International treatment guidelines for anaemia in chronic kidney disease – what has changed? MJA (2), 22July 2013

2. Lerma, E. (2017) Anemia of Chronic Disease and Renal Failure. Emedicine Retrieved October 10, 2017 from emedicine.medscape.com

Causes of Anaemia

Broadly speaking, specific causes of anaemia can be placed into three general categories (see Table 1)

Table 1: Causes of Anaemia (Lerma, E. 2017)

Specific Cause	General Cause (Mechanism)	Examples
Reduced normal RBC production	Erythropoietin deficiency Nutritional deficiencies (Iron, vitamin B12 and folate)	Anaemia of CKD Nutritional Anaemia Inflammation
Increased or premature RBC destruction	Haemolytic anaemia	Autoimmune disease
Blood loss	Acute or chronic	Trauma, blood loss during dialysis, a slow bleeding peptic ulcer

Signs and Symptoms

The common feature of all anaemia is a reduction in circulating red cell mass, which is reflected in a reduction in the Hb and haematocrit (Hct) levels. The cause of the anaemia may influence the rate of fall of Hb. A rapid drop in Hb concentration will generally cause more signs and symptoms than a slow fall in Hb concentration. However, gradual decrease in red blood cells will eventually lead to compensatory responses aiming to reduce hypoxia, and this will affect every tissue and organ in the human body giving rise to a variety of signs and symptoms (Lerma, 2017). The common signs and symptoms of anaemia are summarised in Figure 1.

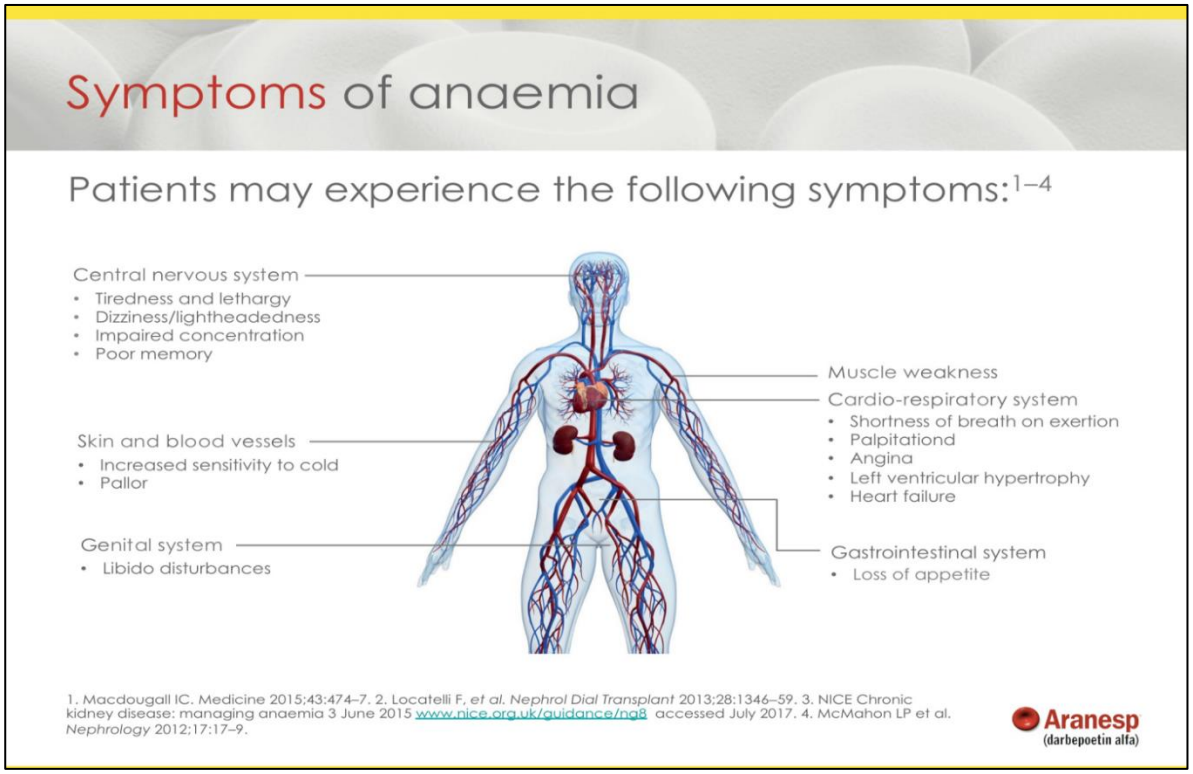


Figure 1: Signs and Symptoms of Anaemia (Diagram with permission of AMGEN Australia)

Diagnostic Tests

Full blood examination or Full blood count (FBC).
Examination of a blood film is useful in determining RBC morphology (shape) and hence, assists in finding the cause of the anaemia. It also allows the number of reticulocytes in the peripheral blood to be measured and other abnormalities to be detected (Lerma, E. 2017). In everyday practice a reduced RBC count and /or a reduced Hct is used as an indicator of anaemia (Schrier, S. 2017).

Haemoglobin (Hb)

Hb is a molecule within RBCs that transports oxygen. The oxygen-carrying capacity of the blood is directly proportional to the Hb concentration (expressed as grams of Hb per litre of blood). The Hb concentration is measured by comparing the colour of a patient's blood to solutions of known Hb concentration. A low value indicates the presence of anaemia but gives no indication of the cause. Serial Hb readings over time allow the progression of the anaemia to be followed, including its response to treatment.

Haematocrit (Hct)

Hct, or packed cell volume, is the percentage of RBCs relative to plasma volume. RBCs are by far the most numerous cells in the blood; hence Hct is used as an indirect measure of RBC count. Packed cell volume (PCV) is another measure of Hct. Hct may be quoted as a percentage (e.g. 40%) or as a decimal (e.g. 0.40).

Table 2: Haemoglobin and Haematocrit Reference Values in Adults.

	Male	Female	Anaemia
Hct	0.42-0.52	0.37-0.47	<0.35
Hb	130-180g/L	115-165g/L	<140g/L (male) <120g/L (female)

Normal ranges of Hb & Hct may not apply to certain populations such as athletes, people living in high altitudes, smokers, African Americans, older adults and people with chronic disease (Schrier, S. 2017).

Morphology

The appearance of RBCs is known as the morphology. The colour, size and shape of RBCs are measured in a standard full blood count (FBC). There are two methods of classifying Anaemia (see Table 4), by the:

- Appearance and number of the RBCs (e.g. normocytic, normochromic)
- Cause of the anaemia (e.g. haemolytic).

Mean Cell Volume

The mean cell volume (MCV) represents the average size or volume of one RBC and indicates whether the cell is:

- Normal - (normocytic)
- Large - (macrocytic)
- Small - (microcytic);

The size of the RBC, combined with other parameters, gives a clue to the cause of the anaemia (see Table 3 for examples).

Table 3: Classification of Anaemia according to appearance of RBC's

	Size (MCV)		
Density (depth of colour/MCHC)	**Microcytic (small)**	**Normocytic (normal)**	**Macrocytic (large)**
Hypochromic	Iron deficiency, chronic blood loss		
Normochromic		Chronic disease, acute blood loss, aplastic anaemia	B12 deficiency, folate deficiency

(Schrier, S. 2017)

LEARNING ACTIVITY

1. Look at your patient's full blood cell count results and compare with normal levels. What differences are there and if any what do they indicate? _____

_____

_____

_____

READING

3. Pagana, K. (2017) Mosby's diagnostic and laboratory test reference. Page 785 – 791.

Mean Cell Haemoglobin (MCH) / Mean Cell Haemoglobin Concentration (MCHV)
(Normal MCH 27-32pg Normal MCHC 310-360g/L).

The mean cell haemoglobin (MCH) represents the amount of Hb in a RBC. Similarly, the mean cell haemoglobin concentration (MCHC) measures the concentration of Hb in each RBC. The Hb concentration gives the cell its degree of redness. A normal-coloured RBC (normochromic) has an MCH > 27pg and an MCHC > 310g/L. The term hypochromia refers to pale RBCs with an MCH < 27pg and/or an MCHC < 310g/L.

Red Cell Distribution Width
(Normal RDW 9 -14, 5%)

The red cell distribution width (RDW) is a measure of the degree of variation of RBC size on a peripheral blood smear. An excessive size variation is called anisocytosis. RDW can be used as an indirect measure of reticulocyte counts,

while an elevated RDW is highly suggestive of iron deficiency anaemia.

Reticulocytes
(Normal 10 -100 x 10/L)

Reticulocytes are erythrocyte precursors that are released from the bone marrow and circulate in the blood as they mature into RBCs. The reticulocyte count indicates the level of erythropoietic activity in the bone marrow. They can be counted manually under a microscope and are commonly expressed as a percentage of the total number of erythrocytes. The reticulocyte count is higher in cases of anaemia where the bone marrow is responsive and producing more RBCs (e.g. after erythropoietin supplementation) and lower when the bone marrow produces fewer reticulocytes (e.g. after chemotherapy).

Other Tests
Other specific tests can be performed to identify the cause of the anaemia such as:

- iron studies
- serum B12
- folate levels
- C-reactive protein (CRP)
- Parathyroid hormone (PTH)

Vitamin B 12 / Folic acid levels
Lack of folic acid and/or cyanocobalamin (Vitamin B12) produces a type of anaemia known as Megaloblastic anaemia. An elevated MCV or MCHC in a FBC suggests this type of anaemia.

C-reactive protein (CRP)
CRP is measured to detect the presence of inflammation.

Parathyroid hormone
Hyperparathyroidism may be related to bone marrow fibrosis.

LEARNING ACTIVITY

2. Anaemia is associated with a reduction in:
   A. RBC numbers
   B. Haemoglobin
   C. Haematocrit
   D. All of the above

3. Complete the table below with examples of types of anaemia:

	Size (MCV)		
Density (Colour/MCHC)	**Microcytic** (Small)	**Normocytic** (Normal)	**Macrocytic** (Large)
Hypochromic			
Normochromic			

Common Types of Anaemia

READING

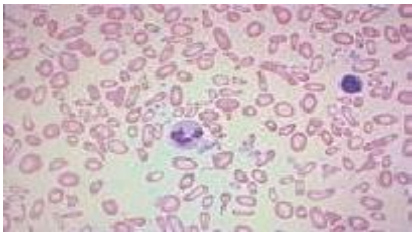
4. Schrier, S. (2017) Approach to the adult patient with anemia. Retrieved 18/10/2017 from http://.www.uptodate.com.hcn.com.au/contents/approach-to-the-adult-patient-with-anemia

Iron Deficiency Anaemia (IDA)

Iron deficiency affects over 12 percent of the world's population, in particular females of child bearing age, children and people living in low to middle income countries. Not all people with iron deficiency develop IDA (Schrier, S. 2017). The major causes of iron deficiency include decreased dietary intake, reduced iron absorption, and blood loss. The RBCs are small (microcytic with a low MCV) and deficient in Hb (as iron is required to form this molecule). Therefore, the RBCs are hypochromic with a low MCHC (Fig.1).

Figure 1. The appearance of RBCs

A: Normal RBCs



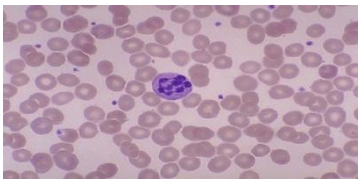
B: RBCs in iron deficiency anaemia

In iron deficiency anaemia, note how the RBCs are smaller (microcytic) and paler (hypochromic) than normal, as well as varying in size (anisocytosis) and shape (poikilocytosis).

Macrocytic Anaemia

Macrocytic anaemia, also known as megaloblastic anaemias, are so named because of the large, oval appearance of the red cell (Figure 2). This occurs because the maturation of the RBC is delayed due to defective DNA synthesis, and it may retain part of its nucleus. The most common causes of macrocytic anaemias that lead to macrocytosis of RBCs are Vitamin B12/Folate deficiency, alcohol toxicity or administration of cytotoxic drugs that impair DNA synthesis (Schrier, S.2017). One example of a malabsorption syndrome causing Vitamin B12 deficiency is pernicious anaemia, in which the stomach is unable to secrete intrinsic factor. Intrinsic factor is required for Vitamin B12 absorption in the terminal ileum.

Figure 2. Appearance of RBCs in Megaloblastic anaemia



Anaemia of Chronic Disease (ACD)

The anaemia of ACD is also known as the anaemia of inflammation (Schrier, S. 2017). In CKD and other chronic metabolic and inflammatory conditions (e.g. cancer and rheumatoid arthritis), the RBCs are typically normochromic and normocytic (normal size, normal Hb content as seen in Figure 1 A above), although mixed pictures can arise if multiple causative factors are present. There is no one definitive test which will reliably make the diagnosis of ACD. However, an array of abnormalities assist to make this diagnosis. This includes: Low serum iron, normal to low serum transferrin level, low transferrin saturation, normal to increased ferritin, elevated CRP level and an elevated hepcidin level (Schrier, S. 2017). Hepcidin levels are generally not attended in the Hunter New England Local Health District.

Haemolytic Anaemia

In patients with haemolytic anaemia, there is premature and/or accelerated RBC destruction combined with RBCs not reaching their usual 120 day lifespan.

The conditions that cause haemolytic anaemia may be either inherited or acquired. Glucose-6-phosphatase deficiency is an example of an inherited disorder in which patients are deficient in a particular enzyme. Certain foods and drugs cause haemolysis of RBCs when patients with this disorder ingest them.

Haemolysis is often due to autoimmune phenomena whereby parts of the red cell surface are identified as foreign by the body's antibodies and destroyed. An example of this is when a drug binds to the surface of a red cell and is recognised by antibodies and removed, as the immune system thinks the RBC bearing this drug is foreign.

People on haemodialysis are at risk of haemolysis (red blood cell destruction) if water used for dialysis is contaminated with chloramine. The haemolysis is acute and maybe life threatening (Nicholas, H. 2017).

Hypo-proliferative anaemia

Describes reduced red blood cell production resulting from a deficiency of one or more key elements required for RBC production for example, erythropoietin or iron.

Aplastic anaemia

Aplastic anaemia is commonly associated with a complete underdevelopment of all cellular components of the bone marrow (i.e. low levels of lymphocytes and other white blood cells). Most commonly, aplastic anaemia is due to chemicals (e.g. benzene), radiation or drugs (e.g. chemotherapy agents). Other commonly used drugs (e.g. antibiotics, anticonvulsants) have been known to cause cases as an idiosyncratic (peculiar or individual) reaction.

Patients with aplastic anaemia are susceptible to severe anaemia (normochromic, normocytic), infection (due to loss of WBCs) and bleeding (due to loss of platelets). The term *pure red cell aplasia* (PRCA) refers to the selective marked reduction or absence of RBC precursors.

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LEARNING ACTIVITY

4. Case study:

Jennifer is 62 years old. Medical history: T2DM for 10 years, hypoglycaemia, iron deficiency, hypertension, stress, dislikes taking tablets, smokes 1-2 packets of cigarettes per week, alcohol intake 1 standard drink per week. She is always tired. After physical assessment pathology is collected for:
FBC, UEC, iron studies and thyroid tests. Investigations reveal:

Test	Result	Reference range
Creatinine (umol/L)	189	50-110
eGFR (ml/min/1.73m2)	33	>90
Hb (g/L)	103	115-165
Iron (umol/L)	7	13-30
Ferritin (ug/L)	298	12-200
TSAT (%)	14	15-45

Discuss possible diagnosis: _____

_____

_____

What illnesses should be excluded? _____

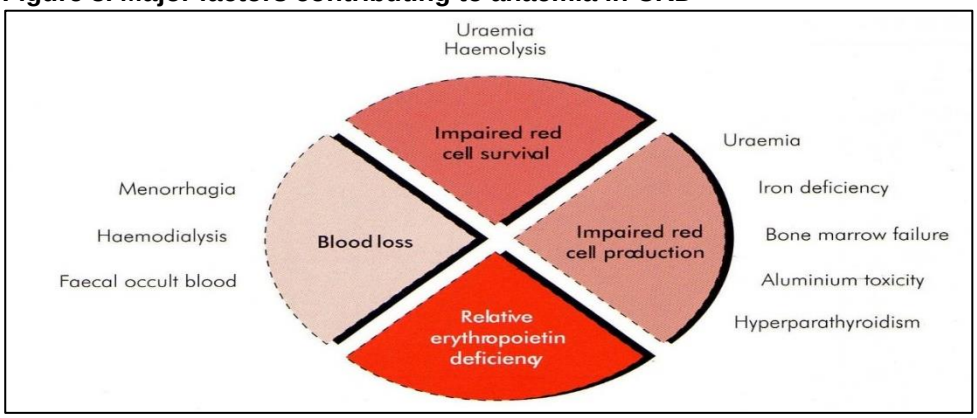
_____

_____

<u>Anaemia of Chronic Kidney Disease</u>

The anaemia of CKD falls under the category of decreased RBC production (Lerma, E. 2017). CKD related anaemia usually occurs at glomerular filtration rates (GFR) of <60mL/min/1.73m² & the prevalence increases markedly with further decline of GFR (KHA, 2012). This anaemia is mainly related to reduction of erythropoietin production by the kidney and resistance to the action of erythropoietin (KHA, 2012).
Morbidity and mortality depends on the underlying aetiology of anaemia and stage of CKD. Management of CKD anaemia should include exclusion and / or treatment of other forms of anaemia, including Vitamin B12, folate and iron deficiency (KHA, 2012).

Figure 3. Major factors contributing to anaemia in CKD



Erythropoiesis

Erythrocytes are unable to divide to replenish their numbers therefore the ruptured cells must be replaced with new cells. The short lifespan of a red blood cell (RBC), being around 120 days, necessitates the process of erythropoiesis which is the formation of red blood cells. Erythropoiesis occurs over a number of stages, most of them in the bone marrow as seen in Figure 4. Once the reticulocyte cells are released into the blood stream it takes 1 - 2 days for them to mature into erythrocytes.

In healthy people the kidneys produce erythropoietin, a hormone essential in the production and regulation of red blood cells in the blood. CKD anaemia normally results from impaired kidney function. This may result in decreased production of endogenous erythropoietin and dysregulation of iron storage and tissue hypoxia (Braunstein, E. 2017).

The amount of erythropoietin normally produced is closely related to the demand for oxygen in the tissues (Lerma, E2017). If oxygen sensors in the kidney detect a lack of oxygen the kidneys increase erythropoietin production.

LEARNING ACTIVITY

5. Copy the slide share web address into your browser and view. www.slideshare.net/1541988/erythropoiesis-51130692

Figure 4: Tissue hypoxia regulates secretion of erythropoietin. (Diagram with permission of AMGEN Australia)

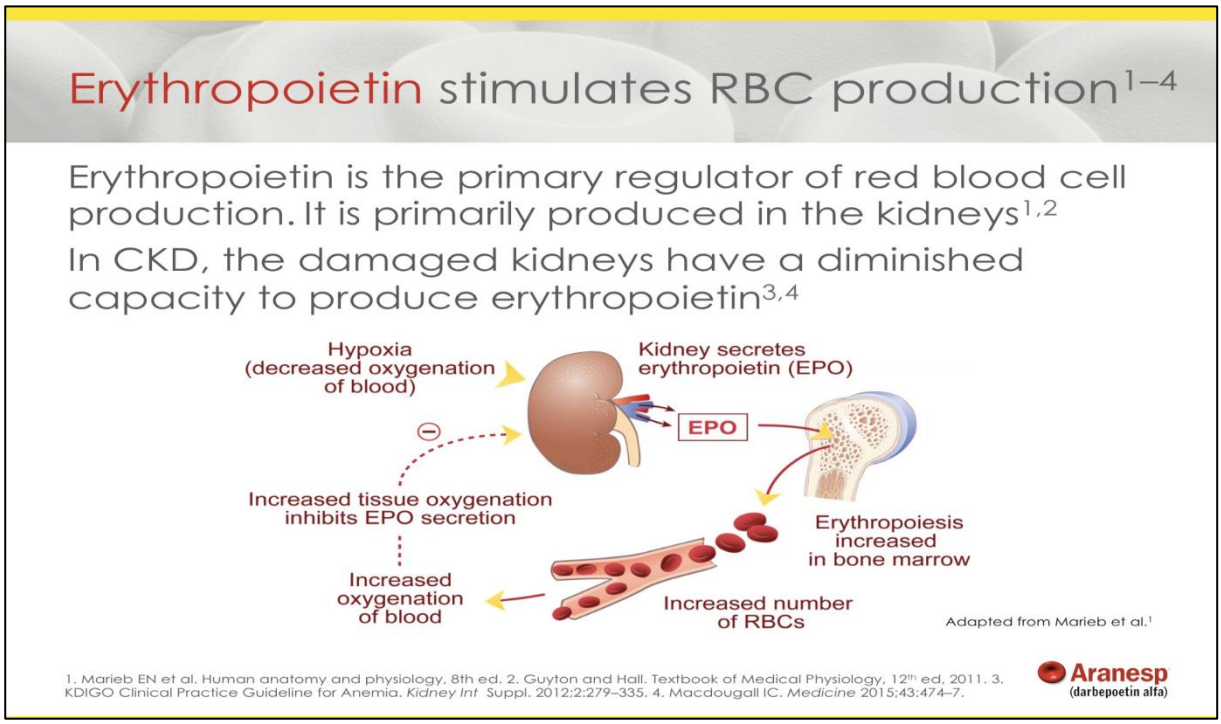
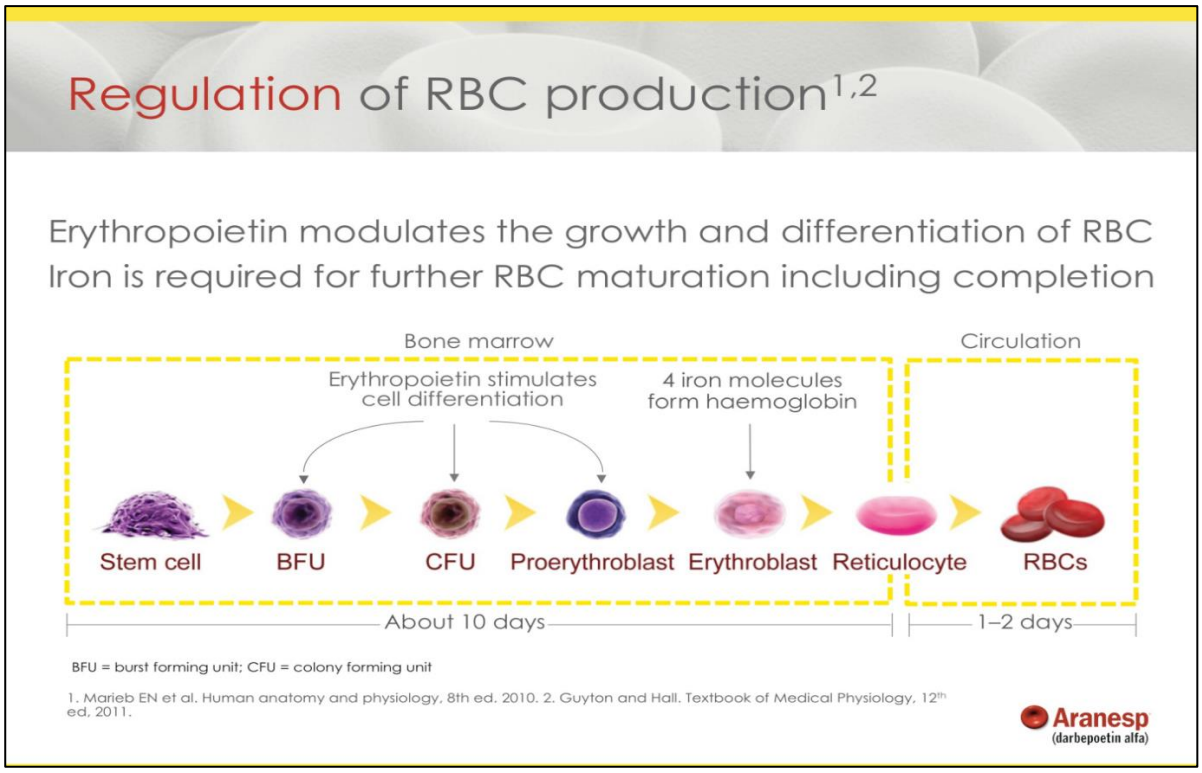


Figure 5. Schematic of Erythropoiesis (Diagram with permission of AMGEN Australia)



Erythropoietin

Erythropoietin Stimulating Agents (ESA)

ESA corrects and improves the disabling symptoms of anaemia, resulting in enhanced quality of life and functional capacity. ESA also reduces the risk of cardiovascular complications of long-standing anaemia.

Erythropoiesis stimulating agents are glycoproteins that are made up of amino acids and sugar molecules and are produced by recombinant DNA technology.

The objective of ESA is to replace the naturally occurring hormone that the body lacks in patients with CKD/ESKD.

There are a number of brands used in the HNELHD including:

- Aranesp (Darbepoetin Alfa).
- Eprex (Epoetin Alfa).
- Mircera (Methoxy Polyethylene Glycol- Epoetin Beta)
- NeoRecormon (Epoetin Beta)

Darbepoetin Alfa is a hyper-glycosylated mutant protein form of erythropoietin. It contains five different amino acids to native erythropoietin. It has a prolonged half-life and approximately three times longer terminal half-life, due to its increased sialic acid–containing carbohydrate content and claims greater in vivo biological activity (MIMS Online- Accessed December, 2017). Epoetin Alfa and Epoetin Beta, on the other hand, have an identical amino acid sequence to endogenous erythropoietin. Epoetin alfa and Epoetin Beta are described as being structurally and functionally indistinguishable from the body's own erythropoietin, which is deficient in patients with CKD/ESKD. Epoetin Alfa has a circulating half-life of approximately 4 - 13 hours in patients with CKD/ESKD and is detectable in plasma for at least 24 hours after administration of an intravenous dose. After IV administration there is a short distribution phase followed by a relatively prolonged elimination phase. Erythropoietin Beta has a half-life of between 4 - 12 hours. Studies reported in the product information claim effective maintenance of haemoglobin levels in patients switched from three times per week administration to once weekly subcutaneous administration, and extended dosing up to fortnightly intervals. The information also states that subcutaneous administration should be considered over intravenous administration as the maintenance dose is lowered by 20 - 35% (MIMS Online- Accessed December, 2017).

Methoxy Polyethylene Glycol-Epoetin Beta is a chemically synthesised erythropoiesis stimulating agent with a much longer half-life than erythropoietin. It shows different activity to recombinant erythropoietin at the receptor level. It is characterised by slower association to the receptor and slightly faster dissociation, resulting in a lower affinity for the receptor. Due to lower affinity, it is slower to eliminate, having a longer half-life than erythropoietin which enables it to be administered in a once monthly dosing regimen (MIMS Online- Accessed December, 2017).

Managing Anaemia in CKD

Previously in Figure 3 major factors that contribute to anaemia in CKD are demonstrated. It is important to monitor and manage contributing factors such as:

- Vitamin B12, iron and folate deficiency
- Occult blood loss
- Chronic infection
- Hyperparathyroidism
- Malnutrition

A number of guidelines are available to assist practitioners manage anaemia in the CKD population via comprehensive evidence based recommendations. These include:

GUIDELINES

1. National Institute for Health and Care Excellence (NICE). Chronic Kidney Disease: Managing Anaemia 2015. nice.org.uk/guidance.ng8
2. Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for Anemia in Chronic Kidney Disease 2012International Society of Nephrology.
3. Caring for Australians with Renal Impairment (CARI).
   Use of Iron in Chronic Kidney Disease 2013
   Biochemical & Haematological Targets: Haemoglobin Levels in Patients Using Erythropoiesis Stimulating Agents 2011; Kidney Health Australia (KHA)

Adequate iron stores are essential to obtain maximum benefit from ESA therapy. Use of oral or intravenous iron is required. Correction of anaemia improves symptoms and has the important effect of reducing cardiovascular complications associated with anaemia. Many patients on haemodialysis receive intravenous iron due to the ease of infusion during the haemodialysis process. Examples of intravenous iron replacement therapies include: Iron Polymaltose (Ferrum-H), Iron Sucrose (Venofer) and Carboxymaltose (Ferrinject).

In 2015 the USA FDA approved Ferric Pyrophosphate (Triferic), a soluble iron replacement therapy, which was added to the haemodialysis solution. Researchers found that Ferric Pyrophosphate was able to maintain haemoglobin and not increase ferritin. At the same time ESA use was markedly reduced in comparison to regular dialysis solution use (Lerma, E. 2017). Looking at MIMS Online there is no information about Ferric Pyrophosphate at this time.

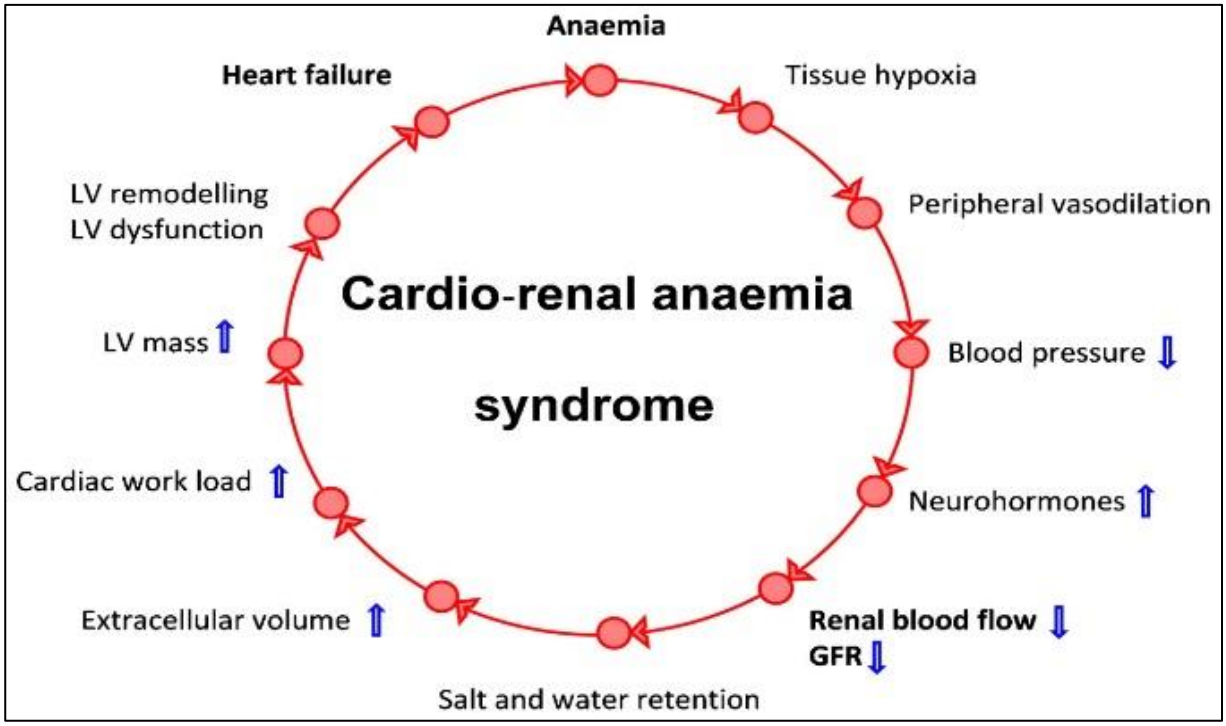
Blood transfusions are not routinely used in patients with CKD. However, once again, investigation & management of contributing factors for anaemia are attended and if anaemia ensues blood transfusion may be indicated.

Effect of ESA on cardiovascular function

Cardio-Renal Anaemia Syndrome

This syndrome refers to a vicious cycle of decreased kidney function leading to lowered ESA production and then anaemia. Anaemia, if severe, leads to left ventricular hypertrophy (LVH). Compensatory LVH ultimately leads to congestive cardiac failure (CHF), which in turn leads to a decline in blood perfusion to the kidneys, resulting in further kidney damage (Lerma, E. 2017).

Figure 6. Cardio-Renal Anaemia Cycle

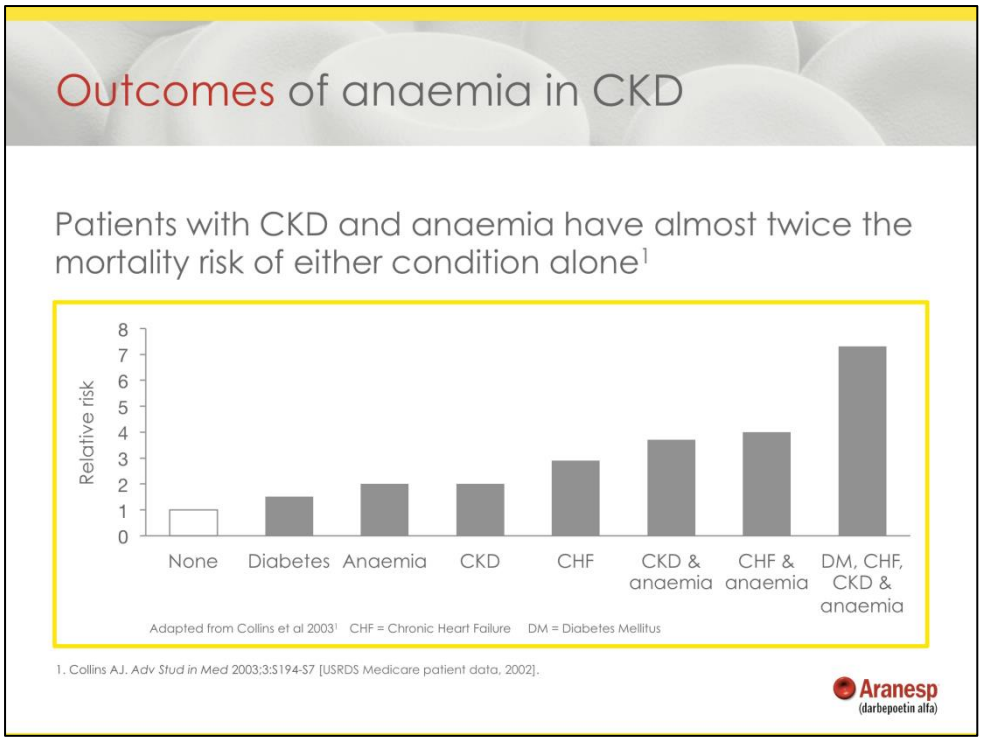


Cardiovascular Disease

As individuals age, the risk of death from cardiovascular disease (CVD) also increases. The influence of anaemia in CVD and CKD in the elderly is concerning and should not be over looked. CVD remains the most common reason of mortality in this patient group. This mortality is much higher than in the general population.

Anaemia has been shown to be an independent risk factor for increased morbidity and mortality (Lerma, E. 2017).

Figure 7: Mortality risk associated with CKD & anaemia (Diagram with permission of AMGEN Australia)



Kidney Health Australia promote comprehensive risk assessment to assist general practitioners to effectively manage their patients with CVD. People with moderate or severe CKD are at the highest risk of a cardiovascular episode. For this group identifying all cardiovascular risk factors present can allow for focused lifestyle & pharmacological interventions (KHA, 2012).

Improvements seen in cardiovascular functioning as a result of ESA administration include:

- Decrease in left ventricular mass
- Decrease in heart rate and cardiac output
- Reduction in cardiac ischaemia

LEARNING ACTIVITY

6. Describe the beneficial effects of ESA on the heart according to the questions on the diagram below.

Left Ventricle:_____

_____

_____

Cardiac Output: _____

_____

_____

Cardiac Ischaemia: _____

_____

_____

7. What is the recommended Hb target for anaemia in CKD/ESKD patients?

_____

_____

ESA hypo-responsiveness

- *Understand hypo-responsiveness to Erythropoietin Stimulating Agents (ESA)*

Erythropoietin stimulating agents are commonly used to treat anaemia associated with CKD. ESA resistance or hypo-responsiveness is a term used to describe patients who do not achieve the preferred haemoglobin concentration despite higher doses of ESA or patients who require progressively higher ESA dosage to maintain haemoglobin concentration (Berna, J. 2017). Several factors including iron deficiency, vitamin deficiency, severe secondary hyperparathyroidism, aluminium toxicity, poor dialysis adequacy, poor nutrition, inflammation and malignancy or haematological disorders have been associated with ESA resistance. Pure red cell aplasia, a condition causing complete ESA resistance has been associated with subcutaneous injection of some ESA brands. These brands are no longer available.

ESA resistance has been associated with increased mortality. This is probably due to the underlying cause of resistance, however, patients receiving higher doses may have increased risk of adverse events including death. (Berns, J.2017).

GUIDELINES

Haematological Targets Guidelines: Biochemical and Haematological Targets: Haemoglobin Levels in Patients Using Erythropoiesis Stimulating Agents, retrieved October 18, 2017, from:

http://www.cari.org.au/DIALYSIS_bht_published/KHA_CARI_Anaemia_guidelines_November_%202011.pdf

Nutritional Supplementation

Ascorbic Acid (Vitamin C) has been used as an adjunct therapy for anaemia in patents receiving ESA (Kim, Y-L, 2012). However, the NICE Guideline (Chronic Kidney Disease: Managing Anaemia, 2015), recommend not prescribing vitamin C, folic acid or carnitine.

LEARNING ACTIVITY

8. What are the causes of hypo-responsiveness to ESA?

_____

_____

_____

9. Read J Berns article and briefly discuss how high levels of PTH reduce patient response to ESA?
https://www.uptodate.com.acs.hcn.com.au/contents/hyporesponse-to-erythropoiesis-stimulating-agents-(ESAs)-in-chronic-kidney-isease

_____

_____

_____

The Effect of ESA on Quality of Life

ESA has a positive effect on quality of life and this has been shown to be true for elderly patients to at least the same extent as for younger patients. In clinical trials, significant improvements have been demonstrated with ESA for most quality of life parameters measured, including:

- functional ability
- sleep and appetite
- health status
- satisfaction with health, sex life and well-being
- psychological effect, life satisfaction and happiness
- energy and activity level

Patients receiving ESA also report improvements in disabling disease symptoms, including weakness and fatigue, shortness of breath and angina as well as cold and pain intolerance. They also show a significant increase in:

- exercise capacity
- energy and vitality
- cognitive function
- well-being

(NICE Guideline -Chronic Kidney Disease: Managing Anaemia, 2015)

Iron

- *Understand the role of iron replacement therapy in the treatment of anaemia associated with chronic disease.*

The iron molecule is central for binding and transporting oxygen by haemoglobin (Hb). Two thirds of the body's iron is found in the Hb of red blood cells (RBCs). One third is stored in the reticuloendothelial cells of the bone marrow, spleen and liver (Pasricha et al, 2010). Iron is absorbed from the gastrointestinal tract and is regulated by the level of body iron stores, erythropoietin and the extent of erythropoiesis (Table 4 Iron metabolism). Transferrin delivers iron to developing erythroid precursors, as well as to other tissues of the body.

The body's iron is derived from two main sources: diet and the daily destruction of RBCs. RBCs circulate for 120 days before being destroyed in the reticuloendothelial system. Iron from the destroyed cells is 'recycled' back to the blood as transferrin.
Figure 8 shows that iron loss occurs through sloughed mucosal cells, desquamation, menstruation and other blood loss. There is no specific excretory mechanism for iron. Approximately 1mg of iron is lost each day through perspiration, the shedding of skin and mucosal cells, and the gastrointestinal tract. Haemodialysis patients lose an average of 2g of iron each year.

There are two forms of dietary iron: heme and non-heme (Pasricha et al, 2010). Iron in meat, fish and poultry is found in a chemical structure known as heme. Heme iron is absorbed efficiently by the body. Iron in plants such as lentils and beans are arranged in a different chemical structure called non-heme iron. Non-heme iron is not as well absorbed as heme iron.

Table 4: Iron utilisation, metabolism and storage.

Utilisation of Iron	Iron metabolism	Storage of iron
Diet usually contains 10-20 mg/day	Iron bound to transferrin, circulates in bloodstream	Ferritin, a protein for the specialized storage of iron in tissues (pool 2.1 g)
Intestinal absorption 1-2 mg/day	Iron is used in the erythroid marrow to produce new RBCs 25 mg/day	Reticuloendothelial system includes spleen & bone marrow (as haemosiderin) 25 mg/day

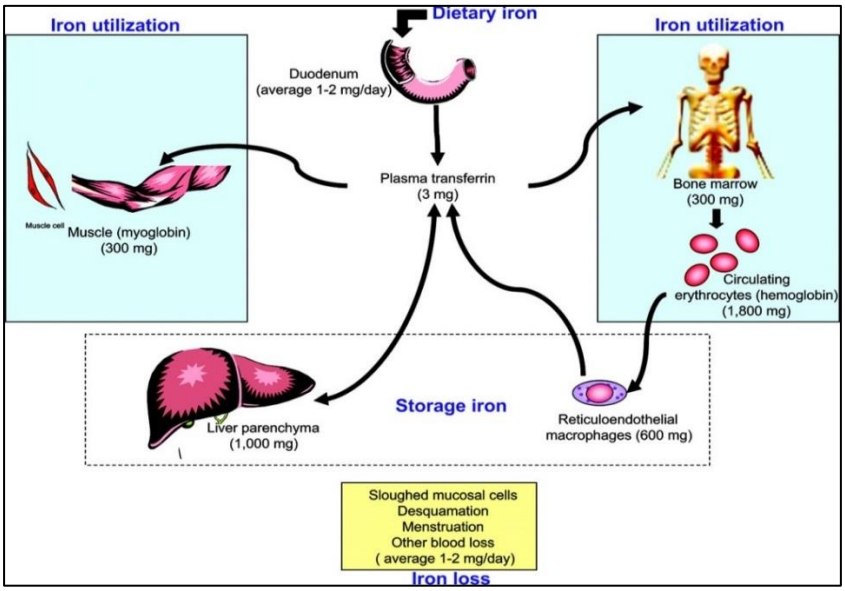


Figure 8: Iron utilisation, metabolism and storage.

Iron deficiency

Iron deficiency is the most common nutritional deficiency in Australia. Iron deficiency causes anaemia, but not all people with iron deficiency are anaemic.
The fall in iron stores progresses through three stages:

- Stage 1: Lowered iron stores
- Stage 2: Iron depletion
- Stage 3: Iron deficiency anaemia.

Iron deficiency can be classified as either absolute or functional:

- **Absolute - Inadequate iron stores**
  Ferritin: < 100 µg/L (no ERT)
  Ferritin: < 300 µg/L (on ERT)
  TSAT: < 20%
- **Functional - Adequate stores, however iron is not delivered quickly enough to developing RBCs**
  Ferritin: > 100 µg/L (no ERT)
  Ferritin: > 300 µg/L (on ERT)
  TSAT: < 20%

Iron deficiency impairs Hb synthesis. In people with normal renal function, it is usually due to excessive blood loss or poor diet.

Ferritin

Ferritin is a protein responsible for the cellular storage of iron. Plasma ferritin is a non-iron containing molecule and is found in serum in low concentrations. In general, variations in total body iron stores are reflected in the serum ferritin level. Serum ferritin levels are helpful in diagnosing iron deficiency anaemia, and anaemia of

chronic infection, thalassaemia and haemochromatosis.

Transferrin

Transferrin is the principal plasma protein for transport of iron. Its concentration correlates with the total iron-binding capacity of serum. Transferrin is synthesized in the liver and to a small extent in the reticuloendothelial system and in endocrine glands such as the testes and ovaries. Transferrin is normally saturated with about one third iron. Total Transferrin Saturation (TSAT), measures the levels of transferrin in the blood, and can be calculated by dividing the serum iron level by the total iron binding capacity (TIBC).

Measurement of transferrin levels in serum and other body fluids aids in the differential diagnosis of malnutrition, acute inflammation and infection. It also aids in the assessment of renal function and RBC disorders, such as iron deficiency anaemia, for which it is also useful in monitoring treatment. In iron deficiency anaemia, the transferrin level is increased due to increases in synthesis. High levels can also be found during pregnancy and estrogen administration.

Transferrin Receptor

The transferrin receptor is a transmembrane protein responsible for physiological iron acquisition. It is found on most cells and binds to transferrin molecules. The iron status of the transferrin molecule affects its affinity to the receptor:

- diferric - highest affinity
- monoferric - intermediate affinity
- apoferric - lowest affinity

Iron Replacement Therapy

Iron supplementation can be used to increase Hb levels in iron-deficient patients with mild anaemia. It can also be used in preparation for the commencement of erythropoietin replacement therapy (ERT), for patients who have developed iron deficiency since commencing an ESA, or as a supplement to enhance response to ESA administration.

Oral Iron Therapy

Oral administration remains the first line therapy for iron replacement due to its ease of administration, lower cost and favorable tolerability profile compared with parenteral administration. Iron is best absorbed on an empty stomach, but many people are unable to tolerate this and may need to take it with food. Milk and antacids may interfere with absorption of iron and should not be taken at the same time as iron supplements. The disadvantages of oral iron therapy are:

- suboptimal
- limited absorption
- poor compliance
- tablets vary in elemental iron content
- gastrointestinal (GI) side effects.

Parental Iron Therapy

Parenteral iron therapy includes intramuscular (IM) and intravenous (IV) administration of iron. The major indications for use of parenteral iron products are:

- non-compliance with therapy
- inability to absorb iron from the GI tract
- iron losses that are too great to be replaced by oral therapy
- GI disorders such as inflammatory bowel disease, in which symptoms may be aggravated by oral iron preparations
- Intolerance to oral iron preparations.

The advantage of parenteral iron is that iron may be created rapidly, whereas this may take months to achieve on oral iron therapy.

Intramuscular Iron Therapy

The disadvantages of intramuscular iron therapy include:

- pain at the site of injection
- brownish discoloration of the skin
- muscle sarcomas
- intramuscular bleeding
- variable absorption and bioavailability.

Intravenous Iron Therapy

The most common parenteral forms given intravenously are:

- iron polymaltose
- iron sucrose
- iron carboxymaltose

Reaction to Intravenous Iron

Adverse reactions to intravenous iron range from mild reactions such as malaise, itching, sweating, nausea, emesis and headache to more severe anaphylactoid and anaphylactic reactions:

- anaphylactic - iron dextran (0.7%) preformed dextran antibodies
- anaphylactoid: - breathlessness, wheezing - abdominal/back pain - arthralgia, myalgia - nausea, vomiting – hypotension
- transferrin overload.

CARI Guidelines state there is no indication for oral iron for haemodialysis patients, and that supplements should be given intravenously.

READING

Copy and paste these links into your browser and read the articles

5. http://www.merckmanuals.com/professional/hematology-and-oncology/approach-to-the-patient-with-anemia/red-blood-cell-production
6. http://www.interactive-biology.com/3969/erythropoiesis-formation-of-red-blood-cells/

References & Bibliography

Berns,J.(2017). *Hyporesponse to erythropoiesis-stimulating agents (ESAs) in chronic kidney disease.* Accessed 18.10.2017 from UpToDate. https://www.uptodate.com.acs.hcn.com.au/contents/hyporesponse-to-erythropoiesis-stimulating-agents-(ESAs)-in-chronic-kidney-isease

Braunstein, E. (2017). *Red Blood Cell Production* Accessed online 30/1/2017 http://www.merckmanuals.com/professional/hematology-and-oncology-/approach-to-the-patient-with-anaemia

Hoenich, N. & Ward, R. (2016). Contaminants in water used for hemodialysis. *UpToDate*, Retrieved from www.uptodate.com

International Society of Nephrology (2012). *KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease.* Accessed online via http://www.kidneyinternational.org

Kidney Health Australia, (2012). *Chronic Kidney Disease (CKD), Management in General Practice* (2nd ed.).

Kim, YL. (2012). Vitamin C and functional iron deficiency anaemia in dialysis. *Kidney Research and Clinical Practice* 2012 March: 31(1):1-3

Lerma, E. (2017). *Anemia of Chronic Disease and Renal Failure.* Accessed 19/10/2017 via https://emedicine.medscape.com/article/1389854-overview

MacGinley, R.& McMahon,L. (2011). KHA-C ARI guideline: Biochemical and haematological targets: Haemoglobin targets in patients using erythropoietin-stimulating agents. *Nephrology* 17, 17-19

MacGinley,R. & Walker, R. (2013). KHA-CARI guideline: use of iron in chronic kidney disease patients. *Nephrology* 18, 747-749

MIMMS Online. Accessed December 2017

National Institute for Health and Care Excellence (NICE) (2015). *Chronic kidney disease: managing anaemia.* Accessed online via nice.org.uk/guidance/ng8

Schrier,S. (2017). Approach to the adult patient with anemia. Accessed 18.10.2017 from UpToDate. https://www.uptodate.com.acs.hcn.com.au/contents/approach-to-the-adult-patient-with-anaemia

Schrier,S. (2017). Causes and diagnosis of iron deficiency and iron deficiency anemia in adults. Accessed 18.10.2017 from UpToDate. https://www.uptodate.com.acs.hcn.com.au/contents/causes-and-diagnosis-of-iron-deficiency-and-iron-deficiency-anaemia-in-adults

Schrier,S. (2017).Clinical manifestations and diagnosis of vitamin B12 and folate deficiency. . Accessed 18.10.2017 from UpToDate. https://www.uptodate.com.acs.hcn.com.au/contents/slinical-manifestations-and-diagnosis-of-vitamin-B12-and-floate-deficiency

Learning Package: Reflection on Learning

This document guides your reflection on the extent to which the package meets your professional development needs, and how you plan to apply your learning into practice. This tool is not part of the assessment process, and has been included as a document that you may wish to include in your professional portfolio. Time taken to complete learning package_____

What was your purpose in completing this learning package?

_____

_____

_____

_____

_____

_____

Did you achieve this by completing the learning package?

_____

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_____

Reflecting on the content, what key learning have you obtained?

_____

_____

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_____

_____

_____

What learning will you apply to your practice immediately? How will you do this?

_____

_____

_____

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_____

What learning needs have you identified as a result of completing this learning package?

_____

_____

_____

_____

How do you plan to address these needs?

_____

_____

_____

_____

_____

Signature:_____ Date:_____

Learning Package Evaluation Form

Your feedback regarding this learning package is important to ensure the package meets your learning needs. Please take 5 minutes to answer the following questions to facilitate any change required for future learning packages.

1. The learning outcomes of the learning package were clearly identified Yes No

2. The learning outcomes of the package were appropriate

3. The content provided enabled me to meet the learning outcomes? Yes No

4.The activities motivated my interest in the topic Yes No

5.The activities and workbook questions supported my understanding of the topic

6.The package was presented in a logical manner Yes No

7.The assessment process related to this package was clearly outlined (if applicable) Yes No

8. My most relevant learning outcomes from this package were:

_____
_____

9. The key learning points from this package I can immediately apply to practice include:

_____
_____

10. The least relevant component(s) of this package were:

_____
_____

11 Some suggestions I would like made to improve the package would be:

_____
_____

12. Further comments:

_____
_____

Thank you for your time to complete the evaluation
Please return to:

The relevant CNE/NE/CNC/NP within your area