Anaemia of Chronic Kidney Disease

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Learning Outcomes

1. Learn how to recognise the symptoms of anaemia of chronic disease
2. Become aware of the tests needed to diagnose anaemia of chronic disease
3. Gain an understanding of the pathophysiology of anaemia of chronic disease
4. Have an awareness of the treatments available for anaemia of chronic disease and how to monitor the effectiveness of these treatments.

Introduction

Anaemia is a condition in which the number of red blood cells and their oxygen carrying capacity is insufficient to meet the body’s physiological needs.

Anaemia of chronic disease (ACD) is the second most prevalent form of anaemia worldwide with iron deficiency anaemia being the most prevalent (WHO, 2011). Anaemia develops when haemoglobin (Hb) concentrations are below the recommended thresholds. Normal Hb levels are considered to be 130-180 g/l in adult males and 115-165 g/l in adult, non-pregnant females. WHO (2001) defines anaemia as Hb levels less than 130 g/l for men, less than 120 g/l for non-pregnant women and less than 110 g/l in pregnant women.

ACD is an independent predictor of morbidity and mortality, is associated with higher rates of hospitalisation and reduces quality of life (Silverberg et al, 2003; He & Wen, 2008).

Prevalence

The prevalence of ACD is common but can vary for several reasons. Studies use a variety of different definitions for anaemia. Prevalence will also vary depending on the severity of the disease process associated with anaemia. ACD can go unrecognised and under treated as the symptoms often reflect those of the chronic disease (Ikram & Hassan, 2011).

In chronic kidney disease (CKD) anaemia is common when the GFR is below 45mls/min particularly in patients with diabetes and CKD (Stevens et al, 2007).

Presence of anaemia in heart failure is associated with renal dysfunction, higher CRP, higher NT-proBNP (heart failure biomarker) and longer hospitalisation. In addition women and elderly are at a higher risk of heart failure and anaemia (Stojcjevski et al, 2013). Resolution of anaemia is associated with a favourable 1-year survival (Goode et al, 2012).

The New York Heart Association (NYHA) classifies heart failure symptoms and functional ability into classes with Class I being the least and Class IV being the worst in terms of functional ability. It has been found that severity of anaemia increases as the NYHA Class increases (Drakos et al, 2009).

Limited data is available on the prevalence of anaemia and survival of patients with chronic obstructive pulmonary disease (COPD) (Lainscak et al, 2009). There is some evidence (Kollert et al, 2011) to suggest an impaired long term survival and reduced quality of life. The management involves excluding any curable causes and reducing exacerbations, systemic inflammation and controlling comorbidities (Chambellan et al, 2012).

There is an increasing number of patients with diabetes and anaemia without associated chronic renal disease. The cause of this anaemia is mainly unknown (Adetunji et al, 2008). Anaemia is also common in inflammatory bowel disease (IBD) as a result of iron deficiency and inflammation (Dumitrescu et al, 2014). Chronic inflammation is common in older people resulting in iron deficiency anaemia being particularly prevalent in people over the age of 80 (Fairweather-Tait et al, 2014).

ACD is seen in a number of conditions including cancer, infection and autoimmune conditions (Table 1).
Table 1. Conditions associated with anaemia of chronic disease

<table>
<thead>
<tr>
<th>Infection</th>
<th>Malignancy</th>
<th>Autoimmune conditions</th>
<th>Renal</th>
<th>Cardiac</th>
<th>Respiratory</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Solid tumours</td>
<td>Rheumatoid arthritis</td>
<td>Chronic kidney disease</td>
<td>Chronic heart failure</td>
<td>Chronic Obstructive Airway Disease</td>
<td>Chronic rejection after solid organ transplant</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Haematological malignancy</td>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitic</td>
<td></td>
<td>Inflammatory bowel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td>Systemic Lupus Erythematosus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoidosis</td>
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</tbody>
</table>

The causes of anaemia are complex and result in complicated pathophysiological processes which are difficult to manage. In recent years there have been advances in understanding the pathogenesis of ACD. It is important that health care professionals caring for these patients have an understanding to guide the diagnosis and management of ACD.

**Pathogenesis of ACD**

The anaemia of chronic disease is immune driven and mainly inflammatory in nature. All localised and systemic infections illicit an immune response to combat the invading pathogenic organism (Weiss, 2011). In addition, any chronic condition, such as uraemia present in chronic kidney disease, diabetes and heart failure, produces an inflammatory response. This causes a systemic acute phase immune response and cytokine release by macrophages (Ganz, 2011). During an immune response, macrophages produce cytokines such as interferon-α, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α).

There are three mechanisms that are thought to lead to ACD namely:
- Impaired iron mobilisation and utilisation
- Impaired marrow erythropoietic response
- Shortened red blood cell survival

**Impaired iron mobilisation and utilisation**

Interleukin-6 appears to be the central mediator of anaemia of chronic disease in a range of inflammatory diseases, including renal disease and rheumatoid arthritis. Interleukin-6 induces the expression of hepcidin, a peptide hormone produced by the liver and the key regulator of iron haemostasis (Ganz, 2011).

Hepcidin suppresses the expression of the iron transporter, ferroportin-1, so inhibiting the absorption of iron from the duodenum and the release of iron from the reticuloendothelial system. The combined effect results in functional iron deficiency.

ACD does harbour some advantages in the presence of infections and cancer. The retention of iron within monocytes and phagocytes results in the reduced availability of iron for invading pathogens which need iron for their growth and proliferation (Weiss, 2011).

**Impaired marrow erythropoietin response**

Cytokines, increased levels of IL-1 & tumour necrosis factor a (TNF-a) are implicated by reducing erythropoiesis. The normal response of increased production of erythropoietin in response to decreasing levels of haemoglobin is blunted. A reduction in the quantity of iron available to transferrin also disrupts the process of erythropoiesis (Cullis, 2011).

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*Picture 1: Inflammatory mechanisms in chronic anemia:*
Shortened red blood cell survival

There is limited evidence that supports a reduction in red cell survival in patients with ACD (Weiss, 2011). However in CKD erythrocyte survival is reduced by 30-60%.

Clinical Features

The presentation may be quite subtle in a person already suffering with chronic disease. The presentation may include the new onset or increased symptoms of tiredness, pallor, breathlessness, tachycardia, irritability and reduced cognitive function.

Diagnosis of ACD

ACD is usually normocytic, normochromic however long standing anaemia can give rise to microcytic and hypochromic blood picture. Microcytic anaemia is characterised by smaller than normal red cells due to decreased haemoglobin (De-Loughery, 2014). It is necessary to assess several laboratory parameters (Table 2) together with a clinical assessment when making a diagnosis.

<table>
<thead>
<tr>
<th>Laboratory Marker</th>
<th>ID without anaemia</th>
<th>IDA</th>
<th>ACD</th>
<th>ACD/IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>MCV/MCH</td>
<td>Low</td>
<td>Low</td>
<td>Normal/Low</td>
<td>Low</td>
</tr>
<tr>
<td>Inflammatory Markers</td>
<td>Negative</td>
<td>Negative</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Low</td>
<td>Low</td>
<td>Normal/High</td>
<td>Low</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Serum hepcidin</td>
<td>Low</td>
<td>Low</td>
<td>Raised</td>
<td>Normal</td>
</tr>
</tbody>
</table>

ACD=anaemia chronic disease, ID=iron deficiency, IDA-iron deficiency anaemia, MCH=mean corpuscular haemoglobin, MCV=mean corpuscular volume

In ACD the haemoglobin level is usually not less than 850 g/l. Serum Ferritin an indicator of iron storage is the most commonly used marker for measuring iron deficiency. However ferritin is an acute phase protein which is elevated in cases of infection and inflammatory conditions.

It is recommended that CRP be measured at the same time as a raised CRP is indicative of infection and inflammation. When both serum ferritin and CRP are raised it does not give an accurate measure of iron status. Serum ferritin <100 ug/l indicates iron deficiency. Optimal serum ferritin levels are 200-500 ug/l.

Transferrin saturation (%TSats), an indicator of circulating iron, and serum iron levels are reduced in patients with ACD. Optimal %TSats should be >20% and measured more than once to achieve an average reading. Transferrin levels are increased in iron deficiency anaemia but normal or decreased in ACD. The percentage hypochromic red cells (%HRC) may contribute to the diagnosis of ACD, providing information about iron supply to red cell precursors and whether the need for iron supplementation is required (%HRC >6% indicates iron deficiency).

It is important to remember that people with anaemia are not all iron deficient and also that iron deficiency may occur without anaemia. The prevalence of anaemia and iron deficiency will vary in different populations which means a correlation between the two cannot be applied.

Other causes of anaemia need to be excluded (Weiss & Goodnough, 2005). This includes nutritional deficiencies (folate & Vitamin B12), haemolysis, myelodysplasia syndrome (MDS) and other haematological factors, bleeding from the GI tract and drug side effects.

Anti-platelet, anti-coagulant and aspirin induced gastritis are examples of drug induced iron deficiency. It has also been reported that angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can induce and worsen anaemia especially in people with CKD. These effects stabilise after three months of initiating therapy and resolve 3-4 months after discontinuing therapy (Caramelo, 2007).

A recent study observed the association of Vitamin D deficiency with anaemia in a large population based survey in the USA (Perlstein et al, 2011). This warrants further investigation to see if Vitamin D supplementation can suppress inflammation and improve ACD (Cullis, 2013).

Management & Treatment of ACD

Management strategies should be based on recognised uniform standards and guidelines to ensure people with ACD receive optimum care and avoid variation in practice. However there is an absence of guidelines in many of the conditions associated with ACD except within anaemia of CKD. Several guidelines exist including NICE 2011, KDIGO 2012, and KDOQI 2006 that all provide evidence based guidance on managing anaemia of CKD.

Anaemia affects quality of life and can independently impact on morbidity and mortality in people with conditions associated with ACD (He & Wang, 2009). Whether measures to correct anaemia will improve survival rates remains to be seen.
Studies have shown that treatment of anaemia of CKD can reduce cardiovascular complications, slow progression of renal failure and improve quality of life (Levin, 1999; Silverberg, 2003).

Treatment of the underlying condition will often result in an improvement in anaemia. The advances in the management of many conditions that cause ACD including HIV and rheumatoid arthritis mean that specific correction of anaemia is often unnecessary (Grozel & Mozina, 2012).

Anaemia is associated with significantly increased rates of joint erosion in patients with rheumatoid arthritis and it is suggested (Woodman, 2013) that anaemia could be a useful independent predictor of radiographic progression.

Rheumatoid arthritis patients need systemic therapy. Disease modifying anti-rheumatic drugs such as methotrexate and in more severe cases the biological response modifiers like Tocilizumab which target the IL-6 receptor are used. Both the arthritis and the systemic inflammation that causes ACD are improved by interfering with the IL-6 signal (Aringer, 2011).

There are no national guidelines in this setting and despite anaemia being commonly identified in this group only a minority are investigated further (Balarajah et al, 2012).

In other conditions such as advanced cancer or cardiac and renal failure, the degree of anaemia reflects the severity of the underlying cause, so correction may improve both prognosis and quality of life.

There is growing evidence that iron metabolism is affected by the ageing process. Chronic low grade inflammation and poor diet results in impaired iron absorption and occult blood loss may result from medications (i.e. Aspirin) commonly prescribed for age related diseases.

Small bowel inflammatory disease is a widespread cause of ACD, guidelines for the treatment of iron deficiency in cancer and inflammatory bowel disease recommend first-line treatment with IV iron therapy (Goddard et al, 2011).

With malignant patients anaemia is often associated with chemotherapy treatment because of the myelosuppressive effects of chemotherapy and or cancer itself. For patients with diseases that cannot be reversed, such as chronic kidney disease or patients undergoing chemotherapy alternative strategies are required. Treatment with intravenous iron alone may be beneficial or the use of erythropoiesis stimulating agents (Grozel & Mozina, 2012).

Treatments

Iron

Functional iron deficiency is common in ACD and iron supplementation is an effective treatment. Oral iron preparations can be used but due to side effects they may not be tolerated. Gastrointestinal effects include nausea, constipation and diarrhoea. In addition oral iron preparations can interact with other medications reducing the absorption of iron. Intravenous iron can then be considered.

Safer forms of parenteral iron have become available in recent years and are widely used in the management of renal anaemia (NICE, 2011).

Some studies have shown that intravenous iron alone may improve haemoglobin levels in patients with ACD associated with cancer (Grosel & Mozina, 2012) inflammatory bowel disease and heart failure. In the past few years’ new data on the importance of iron deficiency in heart failure have become available and a number of studies using intravenous iron have shown promising results (Anker et al, 2009).

In the past intravenous (IV) iron was associated with unwanted side effects especially acute flares in people with rheumatoid arthritis (RA). More recently newer IV iron formulations are thought to be less immunogenic and have been used successfully in these patients. IV iron is now recommended for all RA patients who fail to tolerate or respond to oral iron (Tsang et al, 2010).

There is sufficient evidence linking the treatment of IDA with iron therapy in older people to improve health outcomes such as reducing depression and the risk of falls. However, it is important to ensure body iron stores are monitored as increased iron stores can have detrimental effects on the brain related to memory function (Fairweather-Tait, 2014). Brain iron levels are increased in age related degenerative diseases.

There are a number of intravenous iron preparations available (see table 3) Given that all treatments achieve similar outcomes, the choice of treatment may be based on the preparation and equipment cost and the ease and time of administration for the nurse and the patient.

Table 3. Intravenous Iron Preparations (Joint Formulary Committee, 2013)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Maximum Dose</th>
<th>Bolus Frequency</th>
<th>Maximum Single Dose</th>
<th>Rate of Infusion</th>
<th>Test Dose Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmofer® (Iron (III) hydroxide dextran complex)</td>
<td>200mg</td>
<td>Maximum 3 per week</td>
<td>20mg/kg</td>
<td>4-6 hours</td>
<td>Yes</td>
</tr>
<tr>
<td>Ferinject® (Ferric Carboxymaltose)</td>
<td>1000mg</td>
<td>1 per week</td>
<td>1000mg</td>
<td>15 minutes</td>
<td>No</td>
</tr>
<tr>
<td>Monofer® (Iron isomaltoside)</td>
<td>200mg</td>
<td>3 per week</td>
<td>20mg/kg</td>
<td>Up to 1 hour</td>
<td>No</td>
</tr>
<tr>
<td>Venofer® (Iron Sucrose)</td>
<td>200mg</td>
<td>3 per week</td>
<td>200mg</td>
<td>Up to 30 minutes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The European Medicines Agency (2013) have recently published new legally binding recommendations throughout Europe. This followed the highlighted risk of serious allergic reactions following the administration of intravenous iron especially in pregnant women.

Consequently, iron preparations should only be given in an environment where resuscitation facilities are available and administered by health professionals who have been trained to evaluate and manage anaphylactic and anaphylactoid reactions. The benefits of intravenous iron far outweigh the risks, provided adequate measures are taken to minimise the risks of allergic reactions.

Currently there are two iron related studies in progress within the speciality of renal anaemia. The FIND study is investigating the comparative efficacy and safety of intravenous ferric carboxymaltose versus oral iron to treat iron deficiency anaemia in people with chronic kidney disease not on dialysis (Vifor Inc, 2013). The PIVOTAL study is investigating two regimens for administering intravenous iron (high dose and low dose) to haemodialysis patients. This study aims to determine a safe and effective amount of intravenous iron to give to these patients.

The results of these studies will have implications for other specialities who are interested in the possible merits of intravenous iron, such as heart failure and inflammatory bowel disease.

Erythropoiesis-stimulating agents

The use of erythropoiesis stimulating agents (ESA's) are used to treat ACD once iron deficiency has been ruled out or corrected when present. There is considerable experience with these agents in the setting of chronic kidney disease, and more recently heart failure (Cullis, 2013). Patients with rheumatoid arthritis and HIV can also gain benefits from ESA.

Recent concerns on the safety of ESA in patients with chronic kidney disease have been highlighted. As a result normalisation of haemoglobin in this group with the use of ESA's should be avoided due to the increased risk of stroke and cardiovascular events (Pfeffer et al, 2009). Further research should provide more answers on the safety of ESA's in heart failure and other patient groups (Veildhusen et al, 2011). Hence, haemoglobin (Hb) level should be kept below 120 g/l when ESA therapy is used (NICE, 2011).

Data also suggests an increased risk of tumour recurrence in patients with cancer who receive ESA's. Hence, there are limits on which patients with cancer may receive ESA agents (NICE, 2009).

People receiving maintenance ESA therapy are prone to functional iron deficiency as a result of intense erythropoiesis and are likely to need intravenous iron supplementation to maintain haemoglobin. For patients who are unresponsive to an ESA agent, iron deficiency is the likely cause.

Erythropoietin Stimulating agent Preparations available include:

- Epoetin Alfa (Eprex®)
- Darbepoetin Alfa (Aranesp®)
- Methoxy polyethylene glycol epoetin beta (Mircera®)
- Epoetin Beta (NeoRecormon®)

The choice of preparation will take account of the cost, the dosage, the frequency of administration and the patient's choice.

Blood Transfusion

Blood transfusion is a precious resource and carries risks of transfusion transmitted infection, alloimmunisation, iron overload and sensitisation to HLA antigens (Weiss et al, 2005). Blood transfusions should therefore be reserved for patients with severe and life threatening anaemia with haemoglobin <80 g/l. In fact the use of intravenous iron often reduces the need for blood transfusions in ACD (Litton et al, 2013).

Monitoring Treatment

Monitoring the response to intravenous iron and/or ESA agents' is required. Haemoglobin and iron status (serum ferritin and %TSats) should be measured four weeks after therapy and at intervals of four weeks thereafter when ESA agents are used. The dose of the ESA agent will need adjusting when the haemoglobin nears 120 g/l to maintain a level of 100-120 g/l reducing the risk of stroke/cardiac events. It is recommended that serum ferritin should be maintained between 200-500 ug/l and %TSats kept > 20% for anaemia of CKD (NICE, 2011).

In monitoring the effect of these treatments the use of Quality Of Life metrics should be considered. Clinical studies have shown that correction of iron deficiency in inflammatory bowel disease with IV, rather than oral iron is associated with significantly greater rates of response and significant improvements on quality of life (Evstatiev et al, 2011).

Meta-analysis of small RCTS suggests that ESA treatment can improve exercise tolerance, reduce symptoms and have benefits on clinical outcomes in anaemic patients with heart failure. There is evidence to suggest that treatment with intravenous iron for patients with heart failure and iron deficiency improved their symptoms and quality of life (Anker et al, 2009). However larger well designed studies with close attention to dose, attained haemoglobin level and long term outcomes are recommended (Kotecha et al 2011).

Summary

There is a need for a universal definition of anaemia in ACD which may provide better accuracy in measuring the prevalence of ACD. The development of improved biomarkers of iron status are also needed to enable more accurate clarity of anaemia and iron deficiency in the presence of chronic disease.

ACD is common and its diagnosis should prompt the search for an underlying systemic disorder if none is obvious. It is important to exclude other causes of anaemia especially iron deficiency. Treatment of the underlying disease may improve
anaemia but other treatment options include erythropoietin and parenteral iron. When used these treatments must be evaluated and the patient monitored.

Further research is required to determine the effectiveness of these treatments for ACD. An increased body of evidence will provide a better understanding of ACD. This may support the recognition of ACD and the development of specific guidelines to manage ACD in the various conditions alluded to throughout this paper.

Further information and e-learning modules on the management of anaemia in ACD and chronic kidney disease can be found on the Anaemia Nurse Specialist Association website (www.anaemianurse.org).

### Learning follow-up

Future areas of interest include

- The use of iron chelation therapy to induce endogenous erythropoietin production.
- Hepcidin antagonists to overcome the retention of iron in the reticuloendothelial system.
- Hormones or cytokines that might stimulate erythropoiesis under inflammatory conditions (Ikram & Hassan, 2011).
References


