Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 05, May, 2018, Pages 104 - 110, Available @ www.damaacademia.com

Causes of Erythropoietin Hyporesponsiveness in Chronic Kidney Disease

Dhunik Lukitasari[1], Suharjono[2]
Master of Clinical Pharmacy,
Faculty of Pharmacy, Airlangga University,
Surabaya, Indonesia

Abstract
Based on reports from the K/DOQI (2006), note that approximately 5-10% of patients of chronic kidney disease (CKD) has a low response (hyporesponsiveness) against erythropoietin. Effects of erythropoietin hyporesponsiveness such will cause the risk of cardiovascular disease and mortality being higher. The most common cause of erythropoietin hyporesponsiveness is absolute or functional iron deficiency. In addition, there are several other factors that can also cause erythropoietin hyporesponsiveness, such as chronic inflammation, malnutrition inflammation complex syndrome (MICS), the inadequate dialysis, uremia, hyperparathyroidism, aluminium intoxication, blood loss, malignancy, and diseases of the bone marrow disorders. Identification of the related causes of erythropoietin hyporesponsiveness need to know in order to determine the next steps in the management of anemia.
Keyword : *Erythropoietin Hyporesponsiveness, Chronic Kidney Disease, Anemia*.

I. INTRODUCTION

Anemia is one of the complications that often experienced by patients with chronic kidney disease (CKD). This is primarily due to the existence of a connection between the decline in kidney function with erythropoietin production so in end stage renal disease (ESRD), the anemia condition often encountered and it is difficult to be handled (Babitt & Lin, 2012). The number of patients ESRD anemic in America according to data from the U.S. Renal Data System of Annual Data Report (USRDS) in 2015 is around 86%, which 14% patients have levels of Hb ≥ 12 g/dL, 65% patients have levels of Hb 10-12 g/dL, 15% patients have levels of Hb between 9-10 g/dL, and 6% patients have levels of Hb less than 9 g/dL (USRDS, 2015). The impact of anemia in CKD patients known can lower quality of life (QoL). In addition, there were allegations that there is a relationship between anaemia, cardiovascular disease, and death (Kwack & Balakrishnan, 2006). Therefore, the need for the development of the treatment of anemia in patients current CKD is continuously performed.

One form of the development in the anemia treatment is a Recombinant Human Erythropoietin (rHuEPO). Recombinant Human Erythropoietin (rHuEPO) is exogenous erythropoietin products which created using recombinant DNA technology and is used for the purpose of stimulating the formation of red blood cells (erythropoiesis). Granting of rHuEPO highly recommended in CKD patients Hb levels with 10 g/dL < because according to some studies, it can decrease blood transfusion needs (KDIGO, 2012). Erythropoiesis stimulating agents (ESA) is another term of rHuEPO and began to be developed in the 1980s. Until now there's been three generations of the ESA developed products. The ESA first generation developed is Epoetin alpha (Eprex ® and Hemapo ®) and beta (Recormon ®). The ESA second generation is Darbepoetin alpha (Aranesp ®) and the ESA third-generation is Continous Erythropoiesis Receptor Activator/ CERA (Mircera ®) (Jelkmann, W., 2007). ESA/ rHuEPO product development gives a fairly substantial benefits for patients ESRD like improved QoL, lowering the need for blood transfusions, and reduces exercise capacity (Kimmel & Patel, 2006, Clement *et al*, 2009, Johansen *et al*, 2010). Based on the literature, it is known that 90% CKD patients has a good response to ESA and 5-10% has a low response against ESA although ESA dose given in high doses (K/DOQI, 2006).

Always use ESA high doses can be a marker of the presence an underlying factor that increases the risk of adverse outcomes, such as inflammatory, and give potential impact adverse effect due to use ESA in high doses. Some studies show that there is a relationship between ESA hyporesponsiveness, poor clinical outcomes, cardiovascular disease, mortality, and progressivitas leading to ESRD (Szczech *et al*, 2008, Kilpatrick *et al*, 2008, Minutolo *et al*, 2012)). Therefore, identifying the cause of the ESA hyporesponsiveness is one step that can give you an advantage, like improve the optimization of management anemia, lower treatment costs, and decrease the risk of adverse effects due to use ESA in high doses (Bamgbola OF, 2011). However the pathogenesis of hyporesponsiveness ESA currently is still not fully understood. Therefore, the review of this article will discuss about common causes of ESA hyporesponsiveness in CKD.

A. Definition about ESA/ rHuEPO Hyporesponsiveness

The European Best Practice Guideline (EBPG) II defines resistance to erythropoiesis-stimulating agents (ESAs) as failure to attain the target Hgb while receiving more than 300 IU/kg/week (subcutaneous route) of rHuEPO or 1.5 μg/kg (subcutaneous route) of Darbepoetin (100 μg/week), or a continued need for such high doses to maintain target Hb (Kwack & Balakrishnan, 2006). Whereas according to the Kidney Disease Outcomes Quality Initiative Guidelines define ESA hyporesponsiveness as the presence of at least one of the following: (i) a significant decrease in the hemoglobin (Hb) level with a constant ESA dose; (ii) a significant increase in the ESA dose requirement to preserve a certain Hb level; (iii) failure of the Hb level to rise above 11 g/dl, despite an ESA dose that is equivalent to an rHuEPO dose greater than 500 IU/kg/week (KDIGO, 2012).

Hyporesponsiveness ESA does not always occur in CKD patients, but sometimes found on a small part of the population (Kwack & Balakrishnan, 2006). The relationship between anemia with ESA hyporesponsiveness is multifactorial. The main factors of the alleged cause of the ESA hyporesponsiveness is iron deficiency. However, in some patients ESRD, ESA hyporesponsiveness still persists although it had been given iron supplements, it is suspected as there are chronic inflammatory factor (Ogawa & Nitta, 2015). Other factors also have an influence on the ESA hyporesponsiveness is inadequate dialysis, blood loss, malnutrition, aluminum intoxication, and bone marrow disease (Ogawa & Nitta, 2015).

B. Iron Deficiency

The most common cause of ESA hyporesponsiveness is iron deficiency absolute or functional. Iron deficiency was shown to be present in as many as 25–37.5% of CKD patients presenting with anemia. Enhanced iron utilization due to EPO-induced red blood cell formation can quickly deplete iron stores, especially if previously reduced by poor iron absorption, occult gastrointestinal bleeding, or dialysis-related blood losses. Because of ongoing iron losses, the need for iron supplementation is ubiquitous in the ESRD population (Eschbach, 2005).

The diagnosis of iron deficiency in this setting can be somewhat challenging in that the ferritin level is often elevated due to systemic inflammation. Whereas a low serum ferritin level does imply iron deficiency, a high ferritin level cannot be used to rule out iron deficiency. Most workers in this area agree that the saturation of transferrin is a more helpful indicator of iron deficiency. It is estimated that a transferrin saturation of less than 20% has a sensitivity of 100% and a specificity of 80% for iron deficiency in the ESRD population (Priyadarshi & Shapiro, 2006). Absolute iron deficiency is when levels of ferritin ng/100 mL < and ST < 20%, while iron deficiency is functional when the levels of ferritin > 100 ng/mL and ST < 20% (K/DOQI, 2006). According to the European Survey on Anemia Management (ESAM) 2003, 34% of ESA-treated patients failed to achieve a Hb level of 11 g/dl, and 51.6% were assessed as having inadequate iron status, defined as a serum ferritin concentration <100 ng/ml and/or a TSAT <20% (or a hypochromic red cell value >10%) (Okazaki *et al*, 2014). Adequate intravenous iron therapy is now widely acknowledged as an important strategy for optimizing the hematologic response to ESAs, and numerous controlled trials have demonstrated the superiority of intravenous over oral iron supplementation in hemodialysis patients. However, the iron injection dose shall not exceed 400 mg/month because it was associated with an increased risk of all-cause and cardiovascular death (Kalantar-Zadeh *et al*, 2005).

Iron uptake from plasma to erythroid precursor cells is regulated by different proteins: transferrin receptor, hemochromatosis (HFE) protein and DMT1 (NRAMP2/DCT1). HFE gene mutations are associated with a reduction in the amount of rHuEPO necessary to support erythropoiesis in HD patients. Conversely, some DMT1 gene mutations are associated with an inhibition of intestinal iron absorption and a decrease in erythroid cell precursor iron uptake, resulting in hypochromic and microcytic anemia (Valenti *et al*, 2008). Hepcidin may also be involved in the pathogenesis of anemia of inflammation (Eleftheriadis *et al*, 2006).

C. Chronic Inflammation

Uremic toxins are implicated in the propagation of proinflammatory cytokines, such as IL-1, IL-6, interferon-γ (IFN-γ), and tumor necrosis factor alfa (TNF-α). These cytokines downregulate the expression of EPO receptors on erythroid progenitors and disrupt iron recycling by blocking its release from reticuloendothelial cells, and by inducing hepcidin synthesis. Inhibition of erythropoiesis by cytokines, such as TNF-α and IFN-γ, is also important for erythropoietin resistance. In CKD patients, elevated levels of IL-1, IL-6, TNF-α and CRP (suggestive of a chronic inflammatory status) have been frequently described (Macdougall & Cooper, 2002). Del Vecchio et al. (2005) reported that cytokine-induced inflammation suppresses bone marrow erythropoiesis in HD patients and is a possible cause of anemia (Del *et al*, 2005). Kalantar-Zadeh et al. (2003) confirmed the strong association between indices of EPO hyporesponsiveness and high levels of inflammatory markers in a larger cohort of 339 HD patients (Kalantar-Zadeh *et al*, 2003). The following are links to the inflammatory process induces anemia :

1. Suppression of erythropoiesis: directly, by the inhibitory effects of pro-inflammatory cytokines: IL-1β and TNF-α stimulate the growth of early progenitors BFU-E, but suppresses the growth of the later stages, inducing apoptosis in CFU-E; indirectly as IL-1β and`TNF-α stimulate the production of INF-γ, known to mediate erythropoiesis suppression.
2. Accelerated destruction of erythrocytes (as referred above in the uremic toxins section) by the reticulo-endothelial macrophages activated by the inflammatory state;
3. Reduction of EPO production: in hypoxic conditions, IL-1β and TNF-α increase the expression GATA and NF-κB, both inhibitory of the transcriptional factors of EPO gene;
4. Impaired iron availability for erythropoiesis: The release of the cytokine Interleukin-6 will stimulate the hepatocyte to release hepsidin. When hepsidin is released, the action of ferroportin is inhibited/blocked. Ferroportin (FPN) is a basolateral membranes in cells, hepatocytes, and enterosit macrophages which serves as the exit of intracellular iron towards the extracellular (iron exporter) so that if the action of Ferroportin is inhibited, iron many are stored in the form of ferritin. In addition, hepsidin also inhibits the action of Divalent Metal Transporter 1 (DMT1). The function of the DMT1 is transporting heme iron (Fe2 +) into enterosit, so that when the action is inhibited, the absorption of iron into the enterosit will be hampered (Riberio *et al*, 2013).

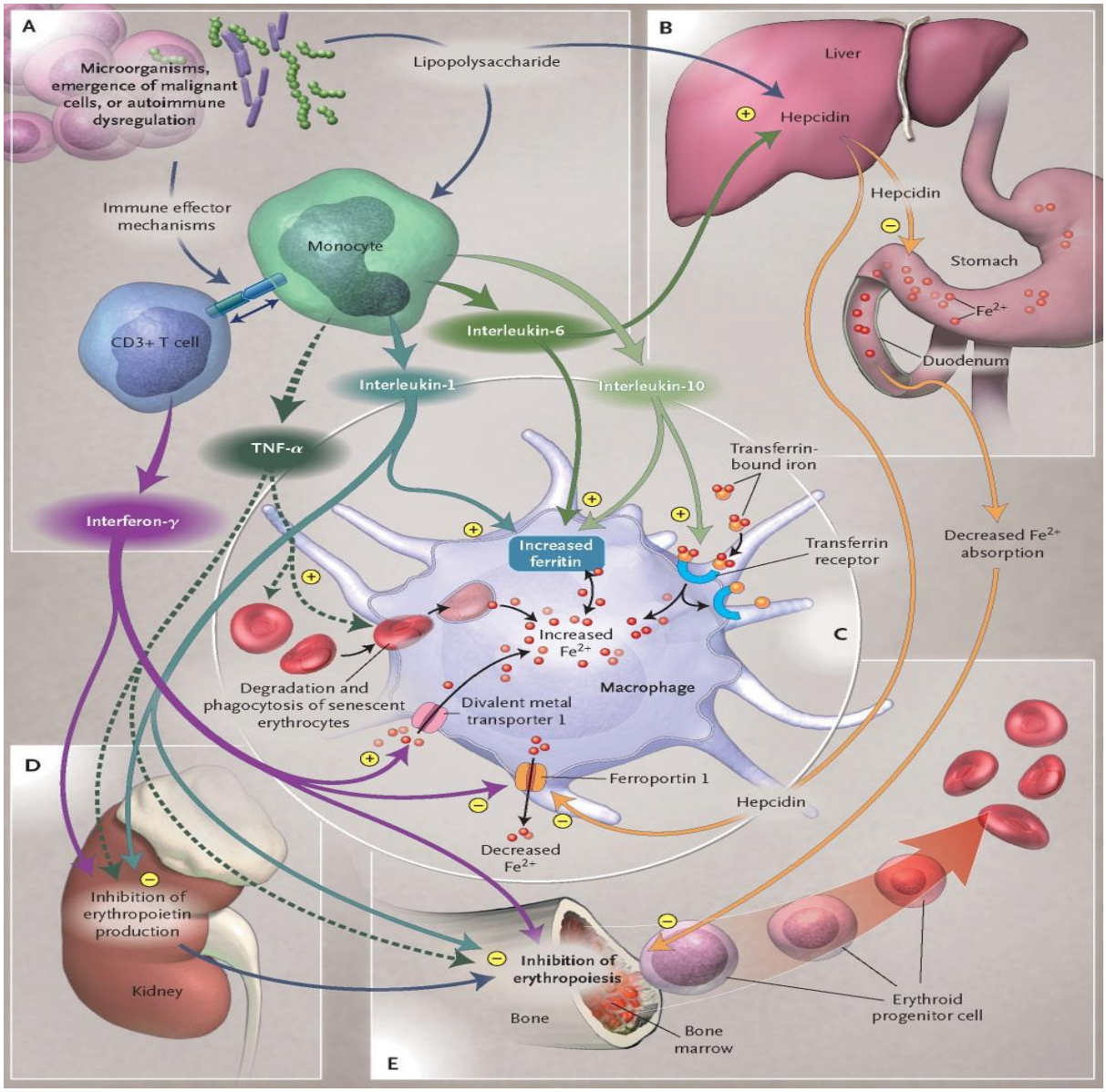

Figure 1. The role of pro-inflammatory cytokines in the process of eritropoeisis (Weiss & Goodnough, 2005).

D. Malnutrition-Inflammation Complex Syndrome (MICS)

Occurring in 35% to 65% of dialysis patients, the primary mechanism of resistance to rHuEpo is typically occult inflammation (Del *et al*, 2005). The association between inflammation, malnutrition, and anemia has been termed the malnutrition-inflammation complex syndrome (MICS) by Kalantar-Zadeh, et al and is typically identified by concurrent elevations in markers of inflammation and depressions in nutritional markers such as albumin and cholesterol (Kalantar-Zadeh, 2003).

Increasing severity of MICS is associated with higher rHuEpo requirements. MICS is also associated with an elevation in serum ferritin concentration, which may lead to reluctance on the part of physicians to administer iron. Although the pathophysiology of MICS is poorly understood, the end result of MICS is not only rHuEpo resistance but also cachexia, increased rate of atherogenesis, higher mortality, and diminished quality of life (Kalantar-Zadeh, 2003). The hemoglobin level is strongly related to the serum albumin concentration as well as markers of inflammation such as tumor necrosis factor α (TNF-α) and interleukin (IL)-6 (Agarwal *et a*, 2008; Keith-Reddy *et al*, 2008). These cytokines not only suppress erythropoietin production but also inhibit the action of the hormone on erythroid progenitor cells. Because both baseline hemoglobin (Hb) and responsiveness to rHuEpo is directly proportional to the serum albumin concentration, it provides a simple bedside test to detect rHuEpo resistance (Ogawa & Nitta, 2015).

F. Inadequate Dialysis

Adequate dialysis appears to be able to influence the response of the body against the EPO. It is proved by a study conducted by McClellan in the year 2000, using a sample randomly, 7092 ESRD hemodialysis patients in the United States, the results of such research explains that there is a relationship between urea reduction ratio (URR) with doses of EPO and Hb levels, at high levels of the URR, the demand for doses of EPO are lower and there is an increase in Hb (McClellan *et al*, 2000). Other research also examines the relationship between dialysis with a dose of EPO is Ifudu et al. (1996), in a prospective study are explained that there is a relationship between the dose of EPO with weekly Kt/V, the weekly dose of EPO decreased as Kt/V increased in patients receiving inadequate dialysis (ifudu *et al*, 1996). However, when data from randomized controlled trials involving adequately dialyzed hemodialysis patients receiving EPO and iron are considered, the role of dialysis dose remains unclear (Locatelli *et al*, 2000; Richardson *et al*, 2003; Opatrny *et al*, 2002). Based on several such research it is difficult to clarify the relative impact of dialysis dose, flux, and membrane biocompatibility on Hb and doses of EPO. Even so, things to know is dialysis have contributions in inflammation. Endotoxin exposure and other contaminants in water or foreign material such as dialyzers bioincompatible are some of the causes of inflammation in dialysis (Sitter *et al*, 2000).

E. Uremia

Uremia itself may be one of the most prevalent causes of inflammation in renal patients through diverse mechanisms. First, the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase is diminished in uremia. Because the function of these enzymes is to inactivate free-radical species, a lower level of activity provokes higher levels of free radical induced cell injury. The diminished activity of antioxidant enzymes also leads to the activation of the inflammatory cascades that trigger the release of proinflammatory cytokines. Second, high levels of advanced glycation end products (AGEs) and advanced lipooxidation end products are also seen in patients with CKD, which are the result of glucose reacting with proteins. AGEs typically accumulate in patients with diabetes mellitus, but given that kidneys are an important organ for the removal of AGEs, they also accumulate in the setting of renal failure even in the absence of diabetes mellitus. High levels of AGEs are associated with increased levels of inflammatory mediators and advanced oxidation products. Dialysis is not effective at removing them because of their protein-bound nature (Ogawa & Nitta, 2015).

G. Hyperparathyroidism

Secondary hyperparathyroidism has frequently been implicated in ESA hyporesponsiveness, possibly as a result of increased red blood cell fragility, direct inhibitory effects of parathyroid hormone on EPO synthesis and erythroid progenitors, or an indirect effect via bone marrow fibrosis (Kwack & Balakrishnan, 2006) . Mandolfo et al. observed a 20% increase in the Hb level in 19 patients after dialysis following parathyroidectomy, despite a 34% decrease in EPO dosage (Mandolfo *et al*, 1998) . Lee et al. reported comparable results in 32 hemodialysis patients after undergoing parathyroidectomy (Lee *et al*, 2003). Similarly, Neves et al. reported a statistically significant 12% increase in the Hb level without a significant change in ESA dosage in 11 elderly CKD patients with secondary hyperparathyroidism who had been treated for 12 months with regular intravenous calcitriol therapy (Neves *et al*, 2006) . There have been no published studies to date concerning the impact of cinacalcet on anemia associated with secondary hyperparathyroidism (Ogawa & Nitta, 2015).

H. Aluminum Intoxication

Aluminum intoxication is an important cause of anemia in dialysis patients. Aluminum overload can interfere with iron metabolism and with the enzymes involved in heme synthesis, resulting in microcytic anemia and some degree of resistance to rHuEPO therapy (Kwack & Balakrishnan, 2006).

I. Other Factors

Patients with ongoing blood loss, various forms of solid tissue malignancy, and primary bone marrow disorders such as myelofibrosis may manifest rHuEPO-resistant anemia. Infections and other conditions that lead to inflammatory states should also be considered (Kwack & Balakrishnan, 2006).

II. SUMMARY

In summary, the erythropoietin hyporesponsiveness is a condition in which a therapeutic failure occurred in the achievement of a target Hb after receiving more than 300 IU/kg/week rHuEPO subcutaneous route, or 1.5 μg/kg Darbepoetin subcutaneous route, or has a tendency to always need higher doses of ESA in maintaining the target Hb. These conditions are known to have occurred in 5-10% CKD patients who received ESA. The most common cause of ESA hyporesponsiveness is absolute or functional iron deficiency. Therefore, before the giving of the ESA, the first identification of the iron status of the CKD patients experiencing anemia. If it is known that the absolute iron deficiency occurs, the granting of adequate iron injection provides many benefits and can lower the doses of erythropoietin. Other causes of ESA hyporesponsiveness, are chronic inflammatory, malnutrition-inflammation complex syndrome (MICS), inadequate dialysis, hyperparathyroidism, uremia, aluminum intoxication, blood loss, malignancy, and bone marrow disorders.

References

Agarwal, R., Davis, JL, Smith, L. 2008. Serum Albumin is Strongly Associated with Erythropoietin Sensitivity in Hemodialysis Patients. **Clin J Am Soc Nephrol**: 3: p. 98-104.

Babitt, JL. & Lin, HY. 2012. Mechanisms of Anemia in CKD. **J Am Soc Nephrol** : 23: p. 1631–1634.

Bamgbola, OF. 2011. Pattern of Resistance to Erythropoietin-Stimulating Agents in Chronic Kidney Disease. **Kidney Int**; 80: p. 464–474.

Clement, FM., Klarenbach, S., Tonelli, M., Johnson, JA., Manns, BJ. 2009. The Impact of Selecting a High Hemoglobin Target Level on Health Related Quality of Life for Patients with Chronic Kidney Disease: A Systematic Review and Meta Analysis. **Arch Int Med**; 169: p. 1104–1112.

Del, VL, Pozzoni P, Andrulli S, et al. 2005. Inflammation and Resistance to Treatment with Recombinant Human Erythropoietin. **J Ren Nutr** 15: p. 137-141.

Eleftheriadis, T., Kartsios C., Liakopoulos, V., Antoniadi, G., Ditsa, M., Papadopoulos, C., Anifandis, G., Skirta, A., Markala, D., Stefanidis, I. 2006. Does Hepcidin Affect Erythropoiesis in Hemodialysis Patients. **Acta Haematol** 116 : p. 238-244.

Elliott, J., Mishler, D., Agarwal, R. 2008. Hyporesponsiveness to Erythropoietin: Causes and Management. **Advances in CKD** Vol 16: No 2: p. 94-100.

Eschbach, JW. 2005. Iron Requirements in Erythropoietin Therapy. **Best Pract Res Clin Haematol** :18 : p. 347-361.

Ifudu, O., Feldman, J., Friedman, EA.. 1996. The Intensity of Hemodialysis and The Response to Erythropoietin in Patients with End Stage Renal Disease. **N Engl J Med** 334: p. 420–425.

Jelkmann, W. 2007. Recombinant EPO Production. **Nephrol Dial Transplant** : 22 : p. 2749–2753.

Johansen, KL., Finkelstein, FO., Revicki, DA., Gitlin, M., Evans, C., Mayne, TJ. 2010. Systematic Review and Meta-Analysis of Exercise Tolerance and Physical Functioning in Dialysis Patients Treated with Erythropoiesis-Stimulating Agents. **Am J Kidney Dis** 55: p. 535–548.

K/DOQI. 2006. Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. **Am J of Kidney Dis**: 47 (5): SUPPL 3.

Kalantar-Zadeh, K., Ikizler, TA., Block, G, Avram, MM., Koppel, JD. 2003. Malnutrition-Inflammation Complex Syndrome in Dialysis Patients: Causes and Consequences. **Am J Kidney Dis** 42: p. 864-881.

Kalantar-Zadeh, K., McAllister, CJ., Lehn, RS., Lee, GH., Nissenson, AR., Kopple, JD. 2003. Effect of Malnutrition-Inflammation Complex Syndrome on EPO Hyporesponsiveness in Maintenance Hemodialysis Patients. **Am J Kidney Dis** 42: p. 761-773

Kalantar-Zadeh, K., Regidor, DL., Mcallister, CJ., Michael, B., Warnock, DG. 2005. Time-Dependent Associations Between Iron and Mortality in Hemodialysis Patients. **J Am Soc Nephrol** 16: 3070–3080.

KDIGO. 2012. KDIGO Clinical Practice Guideline for The Evaluation And Management of Chronic Kidney Disease. **Kidney International Supplements** : 2 : (Suppl 4), p. 279-366.

Keithi-Reddy, SR., Addabbo, F., Patel, TV., Mittal, BV., Goligorsky, MS.,Singh, AK. 2008. Association of Anemia and Erythropoiesis Stimulating Agents with Inflammatory Biomarkers in Chronic Kidney Disease. **Kidney Int** 74: p. 782-790.

Kilpatrick, RD., Critchow, CW., Fishbane, S., Besarab, A., Stehman-Breen, C., Krishnan, M., Bradbury, BD. 2008. Greater Epoetin Alfa Responsiveness is Associated with Improved Survival in Hemodialysis Patients. **Clin J Am Soc Nephrol** 3: p. 1077–1083.

Kimmel, PL. and Patel, SS. 2006. Quality of Life in Patients with CKD: Focus on End-Stage Renal Disease Treated with Hemodialysis. **Semin Nephrol**; 26: p. 68–79.

Kwack, C.& Balakrishnan, VS. 2006. Managing Erythropoietin Hyporesponsiveness. **Semin Dial;** Vol 19 No 2: p. 146–151.

Lee, CT., Chou, FF., Chang, HW., Hsu, YH., Lee, WC., Liao, SC., Chen, JB. 2003. Effects of Parathyroidectomy on Iron Homeostasis and Erythropoiesis in Hemodialysis Patients with Severe Hyperparathyroidism. **Blood Purif** 21: p. 369–375.

Locatelli, F., Andrulli, S., Pecchini, F., Pedrini, L., Agliata, S., Lucchi, L., Farina, M., La Milia, V., Grassi, C., Borghi, M,, Redaelli, B., Conte, F., Ratto, G., Cabiddu, G., Grossi, C., Modenese, R. 2000. Effect of High-Flux Dialysis on The Anemia of Hemodialysis Patients. **Nephrol Dial Transplant** 15: p. 1399–1409.

Macdougall, I.C. & Cooper, A.C. 2002. Erythropoietin Resistance: The Role of Inflammation and Pro-Inflammatory Cytokines. **Nephrol Dial Transplant** 17, Suppl 11 : p. 39-43.

Mandolfo, S., Malberti, F., Farina, M., Villa, G., Scanziani, M., Imbasciati, E. 1998. Parathyroidectomy and Response To Erythropoietin Therapy in Anaemic Patients With Chronic Renal Failure. **Nephrol Dial Transplant** 13: p. 2708–2709.

McClellan, W., Frankenfield, D., Johnson, C., Owen, W., Rocco, M., Wish, J. 2000. Hematocrit and Erythropoietin Dose are Associated with Dose of Dialysis Among Adult Hemodialysis Patients: Results from The 1998 ESRD Core Indicators Project. **J Am Soc Nephrol** 11: p. 287A.

Minutolo, R., Conte, G., Cianciaruso, B., Bellizzi, V., Camocardi, A., De Paola, L., De Nicola, L. 2012. Hyporesponsiveness to Erythropoiesis-Stimulating Agents and Renal Survival in Non-Dialysis CKD Patients. **Nephrol Dial Transplant** 27: p. 2880–2886.

Neves, PL., Trivino, J., Casaubon, F., Santos, V., Mendes, P., Romao, P., Bexiga, I., Bernard, I. 2006. Elderly Patients on Chronic Hemodialysis with Hyperparathyroidism: Increase of Hemoglobin Level After Intravenous Calcitriol. **Int Urol Nephrol** 38: p. 175–177.

Ogawa, T. and Nitta, K. 2015. Erythropoiesis Stimulating Agent Hyporesponsiveness in End-Stage Renal Disease Patients. **Contrib Nephrol. Basel, Karger**: vol 185 , p. 76–86.

Okazaki, M., Kaomatsu, M., Kawaguchi, H., Tsuchiya, K., Nitta, K. 2014. Erythropoietin Resistance Index and The All-Cause Mortality of Chronic Hemodialysis Patients. **Blood Purif** 37: 106–112.

Opatrny, K., Reischig, T., Vienken, J., Eiselt, J., Vit, L., Opatrna, S., Sefrna, F., Racek, J., Brown. 2002. Does Treatment Modality Have an Impact on Anemia in Patients with Chronic Renal Failure? Effect of low and High Flux Biocompatible Dialysis. **Artif Organs** 26: p. 181–188.

Priyadarshi, A. & Shapiro, J.I. 2006. Erythropoietin Resistance in The Treatment of The Anemia of Chronic Renal Failure. **Semin Dial** 19 : p. 273-278.

Ribeiro, S., Costa, E., Belo, L., Reis, Flávio., S., Alice, S. 2013. rhEPO for the Treatment of Erythropoietin Resistant Anemia in Hemodialysis Patients Risks and Benefits. **Intech**. http://www.intechopen.com/books/hemodialysis

Richardson, D., Lindley, E., Bartlett, C., Will, E. 2003. A Randomized Controlled Study of The Consequences of Hemodialysis Membrane Composition on Erythropoietic Response. **Am J Kidney Dis** 42: p. 551–560.

Sitter, T., Bergner, A., Schiffl, H. 2000. Dialysate Related Cytokine Induction and Response to Recombinant Human Erythropoietin in Haemodialysis Patients. **Nephrol Dial Transplant** 15: p. 1207-1211.

Szczech, LA., Barnhart, HX., Inrig, JK, et al. 2008. Secondary analysis of The CHOIR Trial Epoetin-Alpha Dose and Achieved Hemoglobin Outcomes. **Kidney Int** 74: 791-798.

USRDS. 2015. Annual Data Report Volume 2: ESRD in the United States.

Valenti, L., Valenti, G., Como, G., Santorelli, G., Dongiovanni, P., Rametta, R., Fracanzani, AL., Tavazzi, D., Messa, PG., Fargion, S. 2008. HFE Genotype Influences Erythropoiesis Support Requirement in Hemodialysis Patients: A Prospective Study. **Am J Nephrol** 28, p. 311-316.

Weiss, G. and Goodnough, LT. 2005. Anemia of Chronic Disease. **N Engl J Med**, 352: p. 1011-1023.