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Infection and Inflammation in Patients on Dialysis: An Underlying Contributor to Anemia and Epoetin alfa Hyporesponse

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Continuing Education

Acute or chronic infections or inflammatory conditions can exacerbate anemia in patients on dialysis. The primary goal is to identify and treat the underlying disorder, while minimizing the impact on hemoglobin (Hb) levels. Nurses can be instrumental in minimizing the impact of these conditions by monitoring the longitudinal trends in Hb levels, proactively assessing patients for inflammatory or infectious conditions, and intervening to resolve causative conditions and minimize the impact on anemia.

Goal

Minimize the impact of infection and inflammatory conditions on hemoglobin levels.

Objectives

1. Describe the impact of infection and inflammatory conditions on erythropoiesis.
2. Discuss laboratory trends in patients with chronic kidney disease with infections and inflammatory conditions.
3. List factors in assessing patients with chronic kidney disease for infection and inflammatory conditions.

The relationship between chronic kidney disease (CKD), erythropoietin deficiency, and anemia has been well established. Erythropoietin is an endogenous cytokine that provides the essential stimulus for red blood cell (RBC) production. In the presence of erythropoietin, RBC precursors differentiate, proliferate, and mature, leading to an increase in RBC volume. Inadequate production of erythropoietin by the diseased kidneys is the primary cause of the anemia of CKD (Papayannopoulou, D'Andrea, Abkowitz, & Migliaccio, 2005).

Epoetin alfa, a product of biotechnology, has the same structure and biological effects as native erythropoietin and allows effective treatment of the anemia of CKD. Prior to the availability of Epoetin alfa, severe anemia was widespread among patients on dialysis, and most patients required blood transfusions to treat their anemia. At that time, many patients suffered from debilitating anemia-related symptoms that compromised their quality of life, including muscle weakness, fatigue, shortness of breath, and exercise intolerance (National Kidney Foundation, 2006). Since 1991, the percent of patients with a point-in-time Hb below 11 g/dL has decreased from approximately 84% to 22%, reflecting significant progress in treating this insidious disease (United States Renal Data System [USRDS], 2006).

While these analyses highlight the tremendous progress that has been achieved in treating anemia since the introduction of Epoetin alfa, data indicate that the current method of assessing Hb levels may underestimate the amount of time that patients spend with Hb levels below 11 g/dL. In a recent analysis of more than 40,000 patients on dialysis, data were retrospectively analyzed over a period of 2 years to determine the amount of time patients spent with Hb levels lower than 11 g/dL. The results showed that the mean Hb level for all patients over the course of study was 11.7 g/dL – a statistic that is in agreement with the USRDS data. However, an assessment of whether patients were consistently maintained in the target Hb range found that only 22% of patients had Hb levels of at least 11 g/dL for the entire 6-month study period. Significantly, about 30% of patients spent more than 40% of their time – or about 2 1/2 months – with Hb levels below 11 g/dL during the 6-month period (Ofsthun et al., 2005).

These data indicate that there is still significant opportunity to improve the Hb outcomes in patients on dialysis. Variability in Hb levels in patients on dialysis may be affected by a wide variety of factors that can contribute to an acute or chronic anemia (see Table 1). One of the primary categories of factors that can result in hyporesponse is infection and inflammation. This article

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The Nephrology Nursing Certification Commission (NNCC) requires 60 contact hours for each recertification period for all nephrology nurses. Forty-five of these 60 hours must be specific to nephrology nursing practice. This CE article may be applied to the 45 required contact hours in nephrology nursing.

Table 1
Common Conditions That Can Contribute to Anemia

• Malnutrition
• Inflammation
• Infection
• Blood loss
• Hemolysis
• Iron deficiency
• Oxidative stress
• Dialysis inadequacy
• Secondary hyperparathyroidism
• HIV/AIDS
• PRCA
• Malignancies
• Hematologic disorders
• Concomitant medications

Table 2
Common Inflammatory and Infectious Disorders in Patients on Dialysis

Inflammatory Conditions	Infections
• Pericarditis	• Access site infection
• Diabetic skin ulcer	• Urinary tract infection
• Surgery	• Pneumonia
• Rheumatoid arthritis	• Abscessed teeth
• Gout	• Hepatitis B/C
• Lupus	• HIV/TB
• Inflammatory bowel disease	• Peritonitis
• Malignancy	• Respiratory infection
• Gangrene	• Perinephric abscess
• Fracture	• Soft tissue infection
• Soft tissue trauma	• CMV
• Osteoarthritis	• Wound infection
• Transplant rejection	• Gum disease
• Phlebitis	• Osteomyelitis
• Diverticulitis	
• Paronychiae	
• Cellulitis	

provides an overview of the mechanism and impact of infection/inflammatory-based anemia, and uses a case study to explore the nursing role in managing anemia caused by these conditions.

Cytokines and the Acute-phase Response

Although erythropoietin is the essential growth factor for RBC development, the erythropoietic cascade is modulated by a wide variety of other factors that can impede erythropoiesis when they are released during the acute-phase response that occurs in response to inflammatory or infectious disorders (see Table 2). Hb levels can drop rapidly due to accelerated destruction of erythrocytes by inflammatory-activated reticulocyte macrophages. During the initial acute-phase response, these clear the circulation of erythrocytes coated with immunoglobulins or immune complex (Barany, 2003). However, the primary erythropoiesis-suppressing effect of inflammation/infection is due to the inhibitory effects of proinflammatory cytokines on the erythropoietic cascade. Cytokines such as TNF-α and IL-1 diminish erythroid precursor sensitivity to erythropoietin, resulting in a decrease in new cell production (Barany, 2003).

Cytokines, Hepcidin, and Iron

The acute-phase response also has a significant effect on iron parameters. Cytokines such as IL-1, IL-6, TNF-α, INF-γ, and lipopolysaccharide stimulate a decrease in the iron supply to RBC precursors, primarily at the erythroblast stage of development (Weiss & Goodnough, 2005). The primary iron-sequestering effect of cytokines is elicited by IL-6, which stimulates the release of hepcidin. Hepcidin has been shown to be a critical regulator of iron, and the anemia of inflammation/infection is primarily attributed to hepcidin-induced sequestration of iron in macrophages (McGrath & Rigby, 2004). Although the mechanisms by which hepcidin regulates iron have not been fully elucidated, data indicate that hepcidin blocks both the release of storage iron from macrophages, and the absorption of iron from the gastrointestinal tract (Vyoral, & Petrak, 2005).

Data suggest that the onset of action of hepcidin is very quick. In studies with synthetic hepcidin, serum iron levels fell 57% within 22 hours of administration. This rapid effect can be explained by the fact that the plasma transferrin compartment typically contains only 2 to 4 mg of iron, which must turn over every few hours. Thus, blockade of macrophage iron efflux could lead to a decrease in plasma iron concentrations within hours (Kemna et al., 2005).

Studies in patients on dialysis have shown that hepcidin levels correlate with functional iron deficiency and Epoetin alfa hyporesponsiveness. A representative Italian study of 72 patients on hemodialysis and 78 patients on peritoneal dialysis assessed the relationship between weekly doses of Epoetin alfa and levels of hepcidin, highly sensitive c-reactive protein (CRP), Hb, iron, and ferritin (Pertosa et al., 2005). In a univariate analysis, serum hepcidin concentrations directly correlated with highly sensitive CRP ($r = 0.8$; $P < 0.01$), ferritin ($r = 0.5$; $P < 0.01$), and Epoetin alfa dose ($r = 0.4$; $P < 0.05$). Interestingly, serum hepcidin levels were significantly higher in patients on hemodialysis compared with patients on peritoneal dialysis, despite similar Hb and serum iron levels. However, ferritin levels were significantly higher in patients on hemodialysis as were weekly

Epoetin alfa requirements. The authors suggest that an increase in hepcidin levels during inflammatory disorders causes functional iron deficiency and hyporesponse to Epoetin alfa.

Iron Parameters During Infection/Inflammation

In individuals who are not on dialysis, transferrin saturation (TSAT) levels range from 15% to 50% in females, and 20% to 50% in males. Ferritin levels in individuals not on dialysis range from 10 to 120 ng/mL in females, and 20 to 250 ng/mL in males (Tietz, 1995). Ferritin is an acute-phase reactant that increases in the presence of acute or chronic inflammation due to hepcidin-stimulated sequestration of iron in macrophages. While ferritin levels are generally not a good indicator of iron status in patients on dialysis, the revised NKF-KDOQI™ anemia guidelines provide specific tips for managing iron levels in patients on dialysis. The guidelines indicate that ferritin levels should be maintained $\geq$ 100 g/dL in patients on peritoneal dialysis, and $\geq$ 200 ng/mL in patients on hemodialysis. Despite the questionable utility of ferritin in ascertaining iron status, the NKF-KDOQI™ guidelines state that there is no evidence for routinely maintaining ferritin $>$ 500 ng/mL in patients on dialysis. However, when ferritin is $>$ 500 ng/mL and TSAT is $<$ 20%, the need for IV iron should be determined based on the Hb level, responsiveness to Epoetin alfa, and the individual patient's clinical status. The guidelines recommend integrating the assessment of iron and Hb values in conjunction with Epoetin alfa dose requirements to ensure that the dosing and titration of these medications is accomplished in light of the patient's comprehensive clinical picture. (NKF, 2006).

Data from the most recent Clinical Performance Measures (CPM) report shows that the national average for transferrin saturation as of October-December 2003 was 29.3% (ranging from 27.1% to 32.0% among the 18 Networks). Ferritin levels averaged 596 ng/mL over the same time (ranging from 517 to 660 ng/mL among the Networks). Among the 2% of patients with a transferrin saturation $<$ 20% and mean serum ferritin $<$ 100 ng/mL, only 1% were not prescribed IV iron at least once during the 3-month analysis (Centers for Medicare & Medicaid Services, 2004).

C-Reactive Protein Levels During Infection/Inflammation

Infection and inflammation are frequently heralded by an increase in CRP, which is synthesized primarily by hepatocytes, and increases as early as 4 to 6 hours after injury such as inflammation, trauma, or tissue necrosis. The Centers For Disease Control defines the normal range for CRP as 0.08 to 3.1 mg/L. For patients on dialysis, the NKF-KDOQI™ has defined inflammation as a CRP level greater than 5 to 10 mg/L. Levels of CRP increase more dramatically than other acute-phase proteins, making it potentially useful for clinical evaluations (NKF, 2006). Although this test may provide useful information, it is not assessed routinely by many dialysis facilities.

Nursing Implications For Managing Anemia Resulting from Infection/Inflammation

Patients on dialysis are susceptible to many inflammatory and infectious conditions that can affect hematological parameters. Nurses typically are the front-line clinicians who have the best opportunity to proactively identify these conditions, and are frequently responsible for managing the anemia associated with infection and inflammation, regardless of the physiology or etiology. These conditions can often be detected by assessing laboratory trends and a patient's history and physical status. Longitudinal trending of laboratory values, using a minimum of 3 months of Hb readings, can often proactively identify a condition that is affecting Hb. Infection or inflammation should be suspected whenever there is a simultaneous decrease in Hb and TSAT, accompanied by an increase in ferritin. Whenever possible, the underlying condition should be corrected, and anti-inflammatory or antibiotic therapies initiated or titrated as appropriate.

The inhibitory effect of infection/inflammation on erythropoiesis can usually be overcome in a dose-dependent fashion by administering higher doses of Epoetin alfa (Barany, 2003), and, depending on the patient's status, it may be appropriate to titrate Epoetin alfa doses upward to maintain target Hb levels. For Hb levels that are below 11 g/dL or still within the range but trending downward, the dose of Epoetin alfa should be increased by at least 25%. Once the infection or inflammatory condition is resolved, the Epoetin alfa doses should again be titratated downward to avoid overshooting the Hb target.

Whether and to what extent iron administration is safe and effective during infectious/inflammatory conditions still remains undecided. The 2006 NKF-KDOQI™ guidelines recommend discontinuing IV iron during an active infectious process. The guidelines do not preclude use of IV iron if, in the clinician's judgment, a trial of iron therapy is warranted (NKF, 2006).

Nursing implications for management of anemia during infectious/inflammatory conditions are highlighted in the following case study.

Case Study

JB is a 71-year-old female with ESRD caused by diabetes. Concomitant conditions include hypertension, peripheral vascular disease, and congestive heart failure. Her Hb had been relatively stable at a level of 11.8 to 12.4 g/dL for the past 3 months. However, trend analysis detected a gradual decrease in Hb to 11.1 g/dL, accompanied by an increase in serum ferritin from 345 to 815 ng/mL, and a decrease in trans-

ferrin saturation from 32% to 21%. The patient has a history of diabetic foot ulcers.

The patient's temperature is normal, and no reason for the change in laboratory parameters was evident following a routine physical examination (including an examination of the feet, vascular access site, and mouth). The nurse had a discussion with the patient, who mentioned that her right calf had felt warm and painful to the touch for the past week. An examination and diagnostic studies revealed deep vein thrombosis.

After a discussion with the physician, systemic anticoagulation was initiated, the Epoetin alfa dose was increased by 25%, and the frequency of Hb assessments was increased to weekly. The Hb continued to decline to 10.9 g/dL before stabilizing and increasing to 11.3 g/dL in response to the dose increase. Four weeks later, the deep vein thrombosis had resolved, and the Hb again began to increase. The dose of Epoetin alfa was decreased by 25%, and the Hb stabilized at 12.1 g/dL.

Discussion

Patients on dialysis typically have an abnormal immune response and frequently do not exhibit an increase in temperature in the presence of an infectious and inflammatory disorder. Physical examinations are therefore crucial to assess common sites of infection or inflammation. Routine evaluation of vascular access sites for all patients and the feet of patients with diabetes should be undertaken since these are obvious sources of infection or inflammation. Nurses should be cognizant that inflammatory processes can arise in any bodily system, making routine head-to-toe physical examinations a necessity. The patients often can provide the most valuable information regarding their status.

In this case, a quality improvement effort was undertaken to stress the importance of nurses conducting routine head-to-toe physical examinations, and of all staff members routinely querying the patient regarding changes in status.

Conclusion

Acute or chronic infectious or inflammatory disorders can cause or exacerbate anemia, thereby leading to a diminished response to Epoetin alfa therapy and a decrease in Hb. The primary goals in managing the anemia of infection and inflammation to identify and treat the underlying disorder, while minimizing the impact on Hb levels. Nurses can be instrumental in minimizing the impact of these conditions by monitoring the longitudinal trends in Hb levels, proactively assessing patients for inflammatory or infectious conditions that may cause anemia, predicting their clinical course, and intervening to resolve causative conditions and minimize the impact on anemia.

References

Barany, P. (2003). Inflammation and resistance to erythorpoiesis-stimulating agents – Links to oxidative stress and cardiovascular mortality. Retrieved May 16, 2006, from www.uninet.edu/cin2003/conf/barany/barany.html

Centers for Medicare & Medicaid Services. (2004). *Annual Report, End Stage Renal Disease Clinical Performance Measures Project*. Baltimore, MD: Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of Clinical Standards & Quality.

Kemna, E., Pickkers, P., Nemeth, E., van der Hoeven, H., & Swinkels, D. (2005). Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS. *Blood, 106*, 1864-1866.

McGrath, H. Jr., & Rigby, P.G. (2004.) Hepcidin: Inflammation's iron curtain. *Rheumatology, 43*, 1323-1325.

National Kidney Foundation (NKF). (2006). KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney diseases. *American Journal of Kidney Diseases, 47*, S1-S146.

Ofsthun, N.J., LaBrecque, J., Keen, M., Youngson, H.I., Krishnan, M., & Lazarus, J.M. (2005). The association of mortality and hospitalization with hemoglobin (Hb) and missed dialysis treatments in stage 5 chronic kidney disease (CKD) patients with and without cardiac comorbidities. Abstract and poster presented at the XLII European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress, Istanbul, Turkey.

Papayannopoulou, T., D'Andrea, A.D., Abkowitz, J.L., & Migliaccio, A.R. (2005). Biology of erythropoiesis, erythroid differentiation, and maturation. In R. Hoffman, et al. *Hematology Basic Principles and Practice* (4th ed) (pp. 267-288). Philadelphia, PA: Elsevier Churchill Livingstone.

Pertosa, G., Simone, S., Corciulo, R., Pontrelli, P., Dalfino, G., & Porreca, F.P. (2005). Hepcidin serum levels, functional iron deficiency and erythropoietin (EPO) hyporesponsiveness in hemo (HD) and peritoneal dialysis (PD). *Journal of the American Society of Nephrology, 16*, 476A.

Tietz, N.W. (Ed). (1995). *Clinical Guide to Laboratory Tests* (3rd ed.) (pp. 234, 376). Philadelphia, PA: W.B. Saunders Company.

United States Renal Data System (USRDS). (2006). *USRDS 2006 annual data report. Atlas of end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Vyoral, D., & Petrak, J. (2005). Hepcidin: A direct link between iron metabolism and immunity. *International Journal of Biochemistry and Cell Biology, 37*, 1768-1773.

Weiss, G., & Goodnough, L.T. (2005). Anemia of chronic disease. *New England Journal of Medicine, 5*, 352, 1011-1023.

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Posttest – 1.0 Contact Hour

Posttest Questions

(See posttest instructions on the answer form, on page 324.)

1. A recent analysis indicates that over a 6 month period, about 30% of patients spend about _____ months with Hb below 11 g/dL.

A. 1.5 months
B. 2.5 months
C. 3.5 months
D. 4.5 months

2. An example of a cytokine that can diminish RBC precursor sensitivity to erythropoietin is

A. Hepcidin.
B. IL-10.
C. IL-8.
D. TNF-α.

3. Hepcidin causes a decrease in iron levels during infection or inflammation by preventing

A. the release of iron from macrophages.
B. the release of iron from old red blood cells.
C. iron from entering developing erythroblasts.
D. iron from entering developing reticulocytes.

4. Iron levels can fall quickly when hepcidin levels are increased because the plasma transferrin compartment typically only contains

A. 0.25 to 0.5 mg. of iron.
B. 0.5 to 1 mg. of iron.
C. 1 to 2 mg. of iron.
D. 2 to 4 mg. of iron.

5. The new KDOQI™ anemia guidelines state that there is no evidence for routinely maintaining ferritin levels above

A. 200 ng/mL.
B. 300 ng/mL.
C. 400 ng/mL.
D. 500 ng/mL.

6. According to the NKF-KDOQI™ guidelines, for patients on dialysis, inflammation is defined as a CRP level greater than

A. 2 to 4 mg/dL.
B. 3 to 8 mg/dL.
C. 5 to 10 mg/dL.
D. 12 to 15 mg/dL.

7. To proactively detect the underlying presence of infectious or inflammatory conditions that may be affecting Hb levels, nurses should review longitudinal trends in Hb using at least _____ months of readings.

A. 1
B. 2
C. 3
D. 4

8. For patients with an infectious or inflammatory conditions whose Hb is trending downward and is predicted to go below 11 g/dL, the dose of Epoetin alfa should typically be increased by _____% until the condition is resolved.

A. 15
B. 25
C. 35
D. 45

9. Infection and inflammation should be suspected in patients who exhibit a

A. decrease in Hb and TSAT and an increase in ferritin.
B. decrease in Hb and ferritin and an increase in TSAT.
C. decrease in Hb and an increase in ferritin and TSAT.
D. decrease in Hb and a decrease in ferritin and TSAT.

10. The most valuable information regarding the source of a potential infectious or inflammatory disorder can often be provided by questioning

A. the nephrologist.
B. the patient care technician.
C. the vascular access surgeon.
D. the patient.

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ANSWER/EVALUATION FORM

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Posttest Instructions

- Select the best answer and circle the appropriate letter on the answer grid below.
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2. a b c d	4. a b c d	6. a b c d	8. a b c d	10. a b c d

Evaluation	Strongly disagree				Strongly agree
1. The objectives were related to the goal.	1	2	3	4	5
2. Objectives were met					
a. Describe the impact of infection and inflammatory conditions on erythropoiesis.	1	2	3	4	5
b. Discuss laboratory trends in patients with chronic kidney disease with infections and inflammatory conditions.	1	2	3	4	5
c. List factors in assessing patients with chronic kidney disease for infection and inflammatory conditions.	1	2	3	4	5
3. The content was current and relevant.	1	2	3	4	5
4. This was an effective method to learn this content.	1	2	3	4	5
5. Time required to complete reading assignment: _____ minutes.					

GOAL Minimize the impact of infection and inflammatory conditions on hemoglobin levels.

I verify that I have completed this activity:

_____
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Comments _____

_____

_____

Suggested topics for future articles? _____

_____

_____