Special Feature

American Society of Nephrology Quiz and Questionnaire 2014: RRT

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Abstract

The Nephrology Quiz and Questionnaire (NQ&Q) remains an extremely popular session for attendees of the Annual Kidney Week Meeting of the American Society of Nephrology (ASN). Once again, the conference hall was overflowing with audience members and eager quiz participants. Topics covered by the expert discussants included electrolyte and acid-base disorders, glomerular disease, end-stage renal disease/dialysis, and transplantation. Complex cases representing each of these categories along with single best answer questions were prepared and submitted by the panel of experts. Prior to the meeting, program directors of U.S. nephrology training programs and nephrology fellows answered the questions through an internet-based questionnaire. During the live session, members of the audience tested their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. They compared their answers in real time using audience response devices with the answers of the nephrology fellows and training program directors (TPDs). The correct and incorrect answers were then discussed after the audience responses and the results of the questionnaire were displayed. As always, the audience, lecturers, and moderators enjoyed this educational session. This article recapitulates the session and reproduces its educational value for the readers of the *Clinical Journal of the American Society of Nephrology*. Enjoy the clinical cases and expert discussions.

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Introduction: Michael J. Choi and Mark A. Perazella (Comoderators)

For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are the most exciting venues of the meeting. The Nephrology Quiz and Questionnaire (NQ&Q) is the essence of clinical nephrology and represents what drew many of us into the field of nephrology. This year's NQ&Q in Philadelphia, with full-house attendance, was no exception. Each of the discussants prepared vignettes of puzzling cases, each illustrating some topical, challenging, or controversial aspect of the diagnosis or management of various areas of nephrology. These eight interesting cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her discussion of the cases.

In this NQ&Q, Rajnish Mehrotra challenges the reader with his two interesting dialysis cases and discusses the appropriate diagnostic and management approaches for these complicated cases. The audience responses are reviewed along with the responses of the training program directors and nephrology fellows obtained before the meeting, giving an interesting perspective into the thought processes of nephrologists with varying levels of training and experience. Rajnish Mehrotra thoughtfully synthesizes the essential clinical, and laboratory data and walks the reader through the diagnosis and management of two complicated cases that highlight challenging issues related to RRTs in patients with ESRD. Overall, it was an educational experience

for all who participated. We hope that this distillate from Atlanta will serve the *CJASN* subscribers well and provide some fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting.

RRT Case 1: Rajnish Mehrotra (Discussant)

A 57-year-old man with ESRD secondary to diabetic kidney disease had been undergoing peritoneal dialysis (PD) for about 6 months. He presented to the dialysis facility having noted cloudiness of the dialysate over the last 24 hours with no associated abdominal pain, fever, nausea, vomiting, or skin rash. He denied constipation or any episodes of touch contamination during connect/disconnect from the cycler over the past few days. His current prescription for PD comprised four exchanges of 2.5 L over 9 hours at night (1.5% and 2.5% dextrose) with 2.5 L 7.5% icodextrin for the 15-hour day dwell. His prescription had been last changed about 8 weeks ago, substituting icodextrin for dextrose-based exchange for the long-day dwell to optimize fluid management. He had a history of long-standing type 2 diabetes mellitus with diabetic retinopathy, gastroparesis, hypertension, and hyperlipidemia. He had been prescribed insulin, enalapril, metoprolol succinate, amlodipine, atorvastatin, sevelamer carbonate, calcitriol, erythropoietin, pantoprazole, and daily application of gentamicin at the exit site.

On examination, he was afebrile and hemodynamically stable. His abdominal examination was characterized by diffuse mild tenderness, with no rebound tenderness, and

normal bowel sounds. The PD catheter exit site was clean and dry, with no drainage or erythema, and there was no tenderness over the tunnel site. There was no skin rash, and the rest of the physical examination was unremarkable.

The PD effluent was sent for testing, and it had a total white blood cell count of 1200 cells/mm^3, with 70% polymorphonuclear cells, 25% eosinophils, and 5% macrophages. The peripheral blood white blood cell count was 10.2×10^3 cells/mm^3, with 62% polymorphonuclear white blood cells, 35% lymphocytes, and 3% eosinophils. The rest of the laboratory tests, including serum chemistry, were unremarkable.

Question 1a
Which of the following would you recommend next?

A. *Oral methylprednisolone taper*
B. *Empiric antibiotic therapy*
C. *Observe without treatment*
D. *Discontinue icodextrin*

Follow-Up
He was started on empiric treatment with cefazolin and ceftazidime pending additional work-up. The results of the gram stain of the PD effluent showed candida species.

Question 1b
Along with initiation of antifungal therapy, which of the following would you recommend next?

A. *Removal of the PD catheter within the next 48–72 hours*
B. *Removal of the PD catheter if inadequate response to antifungal therapy*
C. *Removal of the PD catheter as soon as possible*

Discussion of RRT Case 1
This 57-year-old man undergoing PD has presented with cloudy dialysate, mild abdominal tenderness, and increased effluent white blood cell count. The overwhelming majority of such patients have infectious peritonitis, and hence, empiric initiation of antibiotics in patients with this clinical presentation is always indicated (question 1A, choice B is correct) (Figure 1) (1). In patients with PD-associated fungal peritonitis, the best outcomes are achieved when the PD catheter is removed within 24 hours of presentation, and hence, the catheter should be removed as soon as possible (question 1B, choice C is correct) (Figure 2) (2).

Although the overwhelming majority of patients on PD with cloudy dialysate have infectious peritonitis, occasionally, there are alternative etiologies (Table 1). This patient has several mitigating considerations, making some such alternative causes plausible—the clinical presentation was within 6 months of initiation of PD, with a significantly high proportion of total white blood cell counts in the effluent with eosinophils (idiopathic eosinophilic peritonitis), and he recently transitioned to treatment with icodextrin (icodextrin-induced aseptic peritonitis).

A patient is considered to have eosinophilic peritonitis if >10% of the total white blood cells in the dialysate effluent are eosinophils (3). Single-center case series seem to suggest that idiopathic and infectious PD-related peritonitis comprise 50% each of all patients (3); clinical experience suggests that at least some of these cases may be caused by pneumoperitoneum (4). There are several considerations at the time of presentation that can help make a clinical distinction between idiopathic eosinophilic peritonitis and infectious peritonitis. The probability of patient having infectious PD-related peritonitis is higher with (1) longer interval from the time of initiation of PD to the time of presentation, (2) higher PD fluid cell count, and (3) lower proportion of eosinophils (3). A patient with an effluent white blood cell count ≥2000/mm^3 is highly likely to have infectious peritonitis; conversely, if >30% of the effluent white blood cells are eosinophils, infectious peritonitis is unlikely. It is important to note that none of these criteria are diagnostic and that idiopathic peritonitis is a diagnosis of exclusion.

Idiopathic eosinophilic peritonitis is thought to occur from an allergy to the PD catheter material and usually self-limited. Some case reports have shown success with short courses of steroids or antiallergic medications, such as ketotifen and diphenhydramine. Although presentation 6 months from the start of PD makes idiopathic eosinophilic peritonitis less likely, the total cell count and proportions of cells that are eosinophils are within range for patients with this condition (5–8). However, infectious peritonitis is not an infrequent complication of PD, with high risk for adverse
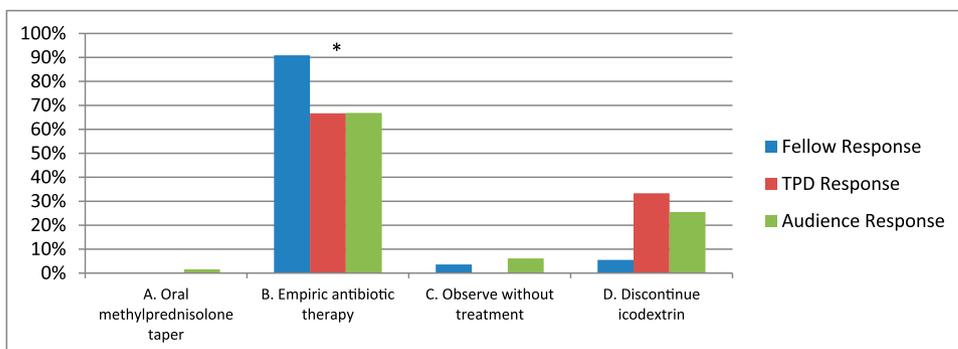

Figure 1. | Answer for Case 1, Question 1a. Which of the following would you recommend next? The correct answer (*) is B. TPD, training program directors.
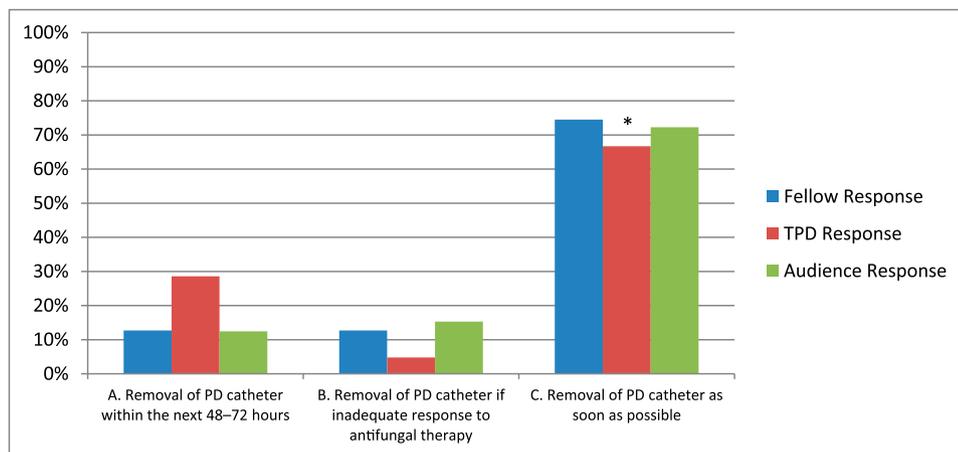
Figure 2. | **Answer for Case 1, Question 1b. Along with initiation of antifungal therapy, which of the following would you recommend next?** PD, peritoneal dialysis. The correct answer (*) is C. TPD, training program directors.

Table 1. Some etiologies of cloudy dialysate in patients undergoing peritoneal dialysis
Infectious peritonitis
Pancreatitis
Chemical peritonitis (*viz.*, aseptic peritonitis with icodextrin)
Malignant ascites
Encapsulating peritoneal sclerosis
Idiopathic eosinophilic peritonitis
Chylous ascites

outcomes without treatment. This makes empiric steroid treatment or expectant observation in lieu of antibiotics as first-line therapy inappropriate (question 1A, choices A and C are incorrect).

Between January and September of 2002, there was a substantial increase in the number of patients treated with icodextrin presenting with aseptic peritonitis (9). Careful investigation of this outbreak has shed light on this now infrequent condition. The data from 186 patients from this outbreak showed that patients with this condition (*1*) do not have fever or other systemic manifestations, (*2*) have, at most, mild abdominal pain, (*3*) have effluent white blood cell count between 300 and 3500 cells/mm^3, (*4*) are virtually never eosinophilic, (*5*) have sterile effluent cultures, and (*6*) improve after withdrawal of icodextrin but recurrence occurs after rechallenge (9). Analyses of dialysate showed a graded increase in the risk for aseptic peritonitis with higher concentrations of peptidoglycan in the lots of bags of icodextrin; lots with ≥60 μg/L peptidioglycan were associated with 253 complaints per million compared with 18 complaints per million with lots with ≤7.4 μg/L (9). Laboratory studies showed that, when the peptidoglycan concentration exceeded 100 μg/L, it induced release of TNF-α and IL-6 and increase in the number of neutrophils in the dialysate (9). Peptidoglycan is a product from the hydrolysis of starch, the process from which icodextrin is manufactured. Since the outbreak in 2002, the manufacturing process has changed,

such that commercially available icodextrin solution has no detectable peptidoglycan. This makes this patient substantially less likely to have icodextrin-associated aseptic peritonitis, and it is inappropriate to discontinue icodextrin as the first-line intervention in lieu of antibiotics (question 1A, choice D is incorrect).

Our knowledge of PD-associated fungal peritonitis is almost entirely on the basis of careful analyses of large case series. Although antibacterial drugs increase risk for fungal peritonitis, up to 40% or more of patients in large case series do not have a history of recent treatment with antibiotics (2,10–13). Patients with fungal peritonitis have a high risk for adverse events, including death (7%–54% in large case series) (Table 2) (2,10–15). Although there are case reports of successful treatment of PD-related fungal peritonitis without catheter removal, patients with catheters left *in situ* have a significantly higher risk for death, making fungal peritonitis an absolute indication for removal of the PD catheter (question 1B, choice B is incorrect) (11,16). In a recent case series, patients in whom the PD catheter was removed >24 hours after presentation had a 13-fold higher risk for death. Hence, it is prudent to remove the PD catheter as soon as possible (question 1B, choice A is incorrect) (2). Other clinical factors associated with a higher risk for death include associated intestinal obstruction, non-Candida infections (such as *Aspergillus* or *Penicillium*), and high peripheral blood and peritoneal white blood cell counts (2,11). Many of the deaths are caused by direct complications of fungal peritonitis (such as overwhelming fungal sepsis or intestinal obstruction) or cardiovascular events (2,10–12,15).

RRT Case 2: Rajnish Mehrotra (Discussant)

A 51-year-old woman with type 2 diabetes mellitus and diabetic kidney disease had recently been initiated on maintenance hemodialysis for the treatment of ESRD through a right internal jugular central venous catheter. About 6 weeks before, she had noticed the appearance of nodular and ulcerating lesions over the skin of her left breast and progressive extensive edema of the left upper extremity. Biopsy of the lesions came back positive for

Table 2.   Reported mortality rates in patients with peritoneal dialysis–related fungal peritonitis

Author, Publication Year (Reference)	Country	Period	Episodes	Mortality (%)
Goldie et al., 1996 (10)	United States	1984–1994	55	20
Wang et al., 2000 (11)	Hong Kong	1989–1998	70	44
Almoujahed et al., 2004 (14)	United States	1998–2001	15	7
Prasad et al., 2004 (12)	India	1993–2001	28	54
Liu et al., 2006 (15)	Taiwan	2001–2003	33	33
Miles et al., 2009 (13)	Australia and New Zealand	2003–2006	162	9
Chang et al., 2011 (2)	Korea	1992–2008	94	29

inflammatory carcinoma of the breast. On the basis of the extent of regional invasion, the oncologist concluded that the only therapeutic option at this time remains palliative chemotherapy, with little probability of cure. She also had a history of long-standing type 2 diabetes, autonomic neuropathy, hypertension, hyperlipidemia, and congestive heart failure. The last echocardiogram had shown a left ventricular ejection fraction of 40%. She had been prescribed lantus insulin, sevelamer carbonate, simvastatin, enalapril, carvedilol, erythropoietin, iron sucrose, and renal vitamins.

On physical examination, her predialysis BP was 150/77 mmHg, and her postdialysis BP was 130/70 mmHg. Her lower extremities had trace bilateral pitting edema, and the rest of her physical examination was unremarkable. Her most recent laboratory tests had shown hemoglobin of 9.2 g/dl, iron saturation of 45%, and ferritin of 689 ng/ml.

Question 2

Which of the following would you recommend regarding the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia in this patient?

A. *No additional administration of ESAs*
B. *Titrate dose to avoid transfusions*
C. *Use unit-specific protocol for the management of anemia*
D. *Titrate dose to minimize decrease in hemoglobin associated with chemotherapy*

Discussion of RRT Case 2

This 51-year-old patient with ESRD undergoing maintenance hemodialysis has incurable breast cancer, for which she is expected to receive palliative chemotherapy. Kidney failure, chronic inflammation from cancer, and myelosuppressive chemotherapy are all likely to result in anemia severe enough to require blood transfusions. ESAs have been shown to result in a decrease in the need for red blood cell (RBC) transfusions, and a treatment plan to administer these agents with the goal of avoiding RBC transfusions is consistent with the product label approved by the Food and Drug Administration for both kidney disease and cancer (choice B is correct) (Figure 3) (17). However, given the increased risk of disease progression and increased mortality in patients with solid tumors treated with ESAs as discussed below, the decision to initiate an ESA and the goals of treatment should be made in partnership with the patient and her oncologist.

Since the initial approval of ESAs by the Food and Drug Administration, the overwhelming majority of patients undergoing maintenance dialysis are treated with this class of drugs. Early clinical trials in patients with kidney disease showed that treatment with ESAs virtually eliminated the need for RBC transfusions that had, thus far, been required every 2–4 weeks for many patients undergoing maintenance dialysis. With observational studies consistently showing a higher risk for death with lower hemoglobin levels in patients with varying severity of CKD, including cardiovascular death, several clinical trials have been undertaken to
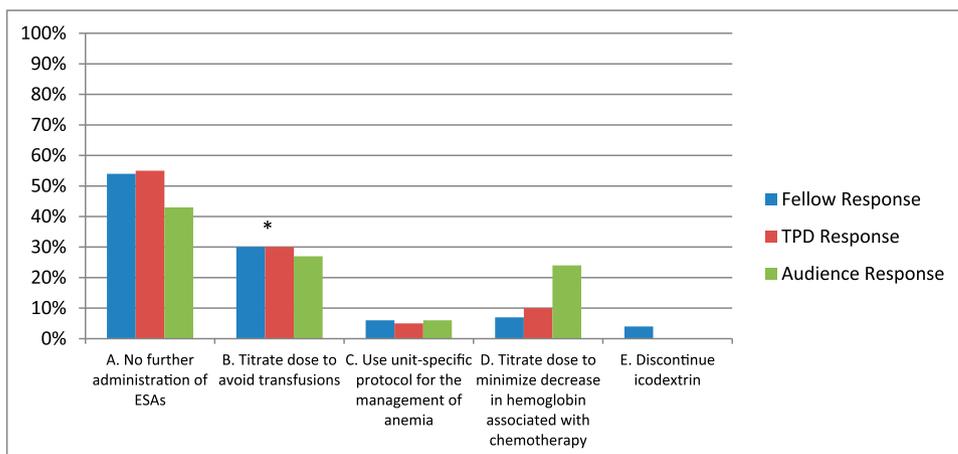

Figure 3. | Answer for Case 2, Question 2. Which of the following would you recommend regarding the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia in this patient? The correct answer (*) is B. TPD, training program directors.

Table 3. Evolution of anemia-related quality measures included in the Quality Incentive Program, a pay-for-performance program for dialysis facilities from the Centers for Medicare and Medicaid Services

Payment Year	Performance Period	Performance Standard: Patient Hemoglobin Levels (%)		Transfusion Measure
		<10 g/dl	>12 g/dl	
2012	2010	2	26	—
2013	2011	—	16	—
2014	2012	—	5	—
2015	2013	—	1	—
2016	2014	—	0	—
2017	2015	—	—	—
2018	2016	—	—	Risk adjusted

determine if this risk can be decreased with higher target hemoglobin for ESA therapy (18–20). Unexpectedly, of four large trials undertaken to test this hypothesis, two trials have shown higher risk for harm in patients assigned to a higher hemoglobin level (higher composite of fatal and nonfatal cardiovascular events in the Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial and higher risk for stroke in the Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT]) (21–24). The third trial and the only one in patients undergoing maintenance dialysis, the Normal Hematocrit Trial, was stopped early, because interim analyses indicated that the study was unlikely to show the hypothesized benefit with higher hemoglobin levels (21). These clinical trials have been highly influential and have dramatically changed clinical practice from target hemoglobin >12 g/dl to a current approach of avoiding RBC transfusions.

These clinical trials also led the Food and Drug Administration to add a black box warning on the product label for ESAs about the risks of adverse vascular events when ESAs are administered to achieve a hemoglobin >11 g/dl (17). The agency warns that no trial has identified a hemoglobin target, ESA dose, or dosing strategy that does not increase these risks or shown an improvement in quality of life, fatigue, or patient wellbeing (17). Hence, ESAs are approved for administration at the lowest dose necessary to reduce the need for RBC transfusions (17). As mandated by congressional legislation, the Center for Medicare and Medicaid Services has structured its pay-for-performance plan for dialysis facilities (Quality Incentive Plan) to include quality measures that facilitate the implementation of the product label for ESAs approved by the Food and Drug Administration (25). Since the introduction of the program in 2012, the quality measures for anemia management have evolved, such that, starting in 2016, only

risk-adjusted transfusion rates for Medicare beneficiaries will be considered (Table 3).

As for patients with CKD, there is high-level evidence that shows that treatment with ESAs reduces the need for RBC transfusions in patients receiving myelosuppressive chemotherapy. In a meta-analysis of 70 trials with 16,093 patients, patients receiving ESAs were 35% less likely to require blood transfusions (26). However, such as in patients with CKD, there is evidence for harm with the use of ESAs in patients with cancer. In one of the first such studies, 939 patients with metastatic breast cancer were randomized to receive 40,000 units every week of erythropoietin or placebo if their baseline hemoglobin levels were <13 g/dl, and they were followed for up to 12 months (27). The mean baseline hemoglobin in this cohort was 12.5 g/dl, and treatment with ESAs was associated with a higher risk for all-cause mortality (27). This risk for harm has been confirmed in subsequent studies, with a meta-analysis showing 6% higher risk for death in patients with solid tumors treated with ESAs (26). Additional adverse events that occur with a higher frequency in patients with solid tumors treated with ESAs include disease progression and venous thromboembolism (26).

As a result of these demonstrable risks, the Food and Drug Administration has also included a black box warning on the product label for ESAs for the treatment of anemia in patients with solid tumors (17). The agency recommends the use of ESAs "for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation there is a minimum of two additional months of planned chemotherapy" (17). As for patients with CKD, the agency recommends use of the lowest dose of ESAs needed to avoid RBC transfusions.

Table 4. Summary of cancer-related adverse events in the entire study cohort and patients with malignancy at baseline enrolled in the Trial to Reduce Cardiovascular Events with Aranesp Therapy

Events	Darbepoietin (n=2012)	Placebo (n=2026)	P value
Cancer–related adverse event	139 (6.9%)	134 (6.4%)	0.53
Cancer-related deaths	39 (1.9%)	25 (1.2%)	0.08
Malignancy at baseline, n	188	160	
All-cause mortality	60 (32%)	37 (23%)	0.13
Cancer-related deaths	14 (2.4%)	1 (0.6%)	0.002

It warns that these drugs should be discontinued on completion of chemotherapy and that the use of these agents is not indicated when the anticipated outcome of the treatment of cancer is cure (17).

There are at least two studies that have examined the risks and benefits associated with ESA administration in patients with both cancer and kidney disease. The TREAT included 4038 patients with type 2 diabetes with a median eGFR of 32 ml/min per 1.73 m^2 who were randomly assigned to darbopoeitin to achieve a target hemoglobin of 13 g/dl or rescue therapy when the hemoglobin reached <9 g/dl (24). There was no significant difference in either cancer-related adverse events or deaths in the entire study cohort (Table 4) (24). In the group of patients with cancer at baseline, although there was no significant difference in all-cause mortality, patients treated with darbopoeitin had a higher risk for cancer-related deaths (Table 4) (24). When the treatment strategy is to avoid the need for RBC transfusions, the target hemoglobin is considerably lower than in the intervention arm of the TREAT. In a second study that examined this issue, the odds for having received treatment with ESAs were compared between 2071 veterans with CKD and stroke and 12,426 controls (28). There was a significant difference in risk for stroke in patients with or without a diagnosis of cancer, with the higher risk for stroke in patients with CKD limited to the subgroup with cancers (28). However, this cohort was derived from a period when the target hemoglobin was considerably higher than would be needed to avoid transfusion.

In the patient under consideration, erythrpooeitin deficiency from ESRD, chronic inflammation from cancer, and the need for myelosuppressive chemotherapy are all likely to result in significant anemia, with a high likelihood for the need for blood transfusions. An approach to administering the lowest dose to avoid RBC transfusions provides a reasonable balance between the benefits and risks from ESAs and blood transfusions. As per the guidance from the Food and Drug Administration, because the goal of chemotherapy in this patient is palliation, there is no absolute contraindication for the use of ESAs (choice A is incorrect) (17). Limited evidence suggests that there is variability in ESA-dosing practices between dialysis providers, and at least some large dialysis organizations now offer physicians the choice of more than one protocol for administration of ESAs (29). Hence, depending on the protocol being used in a dialysis facility, the unit-specific protocol may not be sufficient to ensure that the lowest dose of ESA necessary to avoid RBC transfusions is administered (choice C is incorrect). Finally, the dose needed to prevent decrease in hemoglobin with chemotherapy is likely to be higher than needed to avoid RBC transfusions (choice D is incorrect). Notwithstanding the recommendations, the decisions about whether to proceed and the goal of treatment with ESAs are best made in partnership with the patient and the oncologist.

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