ARTICLE

Epoetin Alfa Resistance: Valuation of a Management Algorithm

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ABSTRACT

Background: Patients who require large doses of epoetin alfa to achieve and maintain a target hemoglobin of 110 to 120 g/L are usually considered epoetin alfa–resistant. The Kidney Disease Outcomes Quality Initiative guidelines suggest that epoetin alfa resistance be considered when subcutaneous epoetin alfa doses exceed 300 IU kg^{-1} $week^{-1}$.

Objective: The objective of this project was to develop and validate an algorithm to guide the identification and management of patients on chronic dialysis with suspected epoetin alfa resistance.

Methods: The algorithm developed was used for 3 consecutive months to identify patients who did not respond to epoetin alfa; to identify the causes of nonresponse, including epoetin alfa resistance; and to guide the management of their cases. Patients were excluded from the final analysis if they did not complete the 3-month follow-up.

Results: Of the 212 patients screened, the algorithm identified 21 who were resistant to epoetin alfa. Of the 16 evaluable patients, 11 achieved their target hemoglobin during the follow-up period. Mean hemoglobin concentrations improved from 92.8 ± 11.0 to 106.9 ± 14.7 g/L (p = 0.0009). The most common causes of epoetin alfa resistance were iron deficiency, chronic infection, inflammation, and dialysis inadequacy. Many patients had more than one cause of epoetin alfa resistance.

Conclusion: The algorithm used in this project can be successfully used to identify epoetin alfa resistance and to manage epoetin alfa therapy for patients on hemodialysis.

Key words: epoetin alfa resistance, hemodialysis, end-stage kidney disease

RÉSUMÉ

Historique : Les patients qui ont besoin de fortes doses d'époétine alfa pour atteindre et maintenir des taux d'hémoglobine cibles de 110 à 120 g/L sont habituellement réputés être résistants à l'époétine alfa. Les lignes directrices de l'Initiative sur la qualité des résultats pour la maladie rénale (Kidney Disease Outcomes Quality Initiative) suggèrent d'envisager une résistance à l'époétine alfa lorsque les doses nécessaires d'époétine alfa sous-cutanée chez un patient dépassent 300 UI kg^{-1} $semaine^{-1}$.

Objectif : L'objectif de ce projet était d'élaborer et de valider un algorithme permettant de dépister et de prendre en charge les patients sous dialyse à répétition, chez qui l'on soupçonne une résistance à l'époétine alfa.

Méthodes : L'algorithme mis au point a été utilisé pendant trois mois consécutifs pour dépister les patients qui n'ont pas répondu à l'administration d'époétine alfa, identifier les causes de l'absence de réponse, y compris la résistance à l'époétine alfa, et aiguiller la prise en charge de ces cas. Les patients étaient exclus de l'analyse finale s'ils n'achevaient pas la période de suivi de trois mois.

Résultats : Parmi les 212 patients sélectionnés, l'algorithme a permis de dépister 21 patients résistants à l'époétine alfa. Des 16 patients évaluables, 11 ont atteint leur taux d'hémoglobine cible au cours de la période de suivi. Les concentrations moyennes d'hémoglobine ont augmenté, passant de 92,8 ± 11,0 à 106,9 ± 14,7 g/L (p = 0,0009). Les causes les plus fréquentes de résistance à l'époétine alfa étaient les suivantes : carence en fer, infection chronique, inflammation et dialyse insuffisante. Chez de nombreux patients, la résistance à l'époétine alfa était due à plus d'une cause.

Conclusion : L'algorithme auquel on a eu recours dans le cadre de ce projet peut être utilisé avec succès pour dépister la résistance à l'époétine alfa et prendre en charge le traitement par l'époétine alfa chez les patients hémodialysés.

Mots clés : résistance à l'époétine alfa, hémodialyse, stade d'insuffisance rénale terminale

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INTRODUCTION

Marketed in the last decade, epoetin alfa (Eprex, Janssen-Ortho Inc., Toronto, Ontario) has improved the quality of life of patients with anemia associated with chronic renal disease.[1] This anemia is primarily the result of inadequate erythropoietin production and other factors such as iron deficiency.[2] Anemia causes cardiac ischemia and left ventricular hypertrophy, both of which predispose patients with chronic renal disease to cardiac morbidity.[3-8] Most patients on chronic dialysis require administration of epoetin alfa for the optimal management and prevention of anemia.

Most patients with chronic renal disease respond to a subcutaneous epoetin alfa dose of 300 IU kg^{-1} $week^{-1}$ (or 450 IU kg^{-1} $week^{-1}$ IV) within 4 to 6 months. However, the epoetin alfa doses required to achieve a target hemoglobin of 110 to 120 g/L vary considerably.[9,10] Patients who require large doses of epoetin alfa to achieve and maintain the target hemoglobin or who do not achieve that target despite large doses are usually considered epoetin alfa–resistant or hyporesponsive.[11,12]

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines define an inadequate response to epoetin alfa as the inability to achieve the target hemoglobin or hematocrit in the presence of adequate iron stores within 4 to 6 months of the initiation of epoetin alfa therapy (450 IU kg^{-1} $week^{-1}$ IV or 300 IU kg^{-1} $week^{-1}$ SC).[10] A more dynamic definition classifies as poor responders those patients whose hemoglobin concentration does not increase more than 10 g L^{-1} $month^{-1}$, despite epoetin alfa doses of more than 200 IU kg^{-1} $week^{-1}$.[12]

The economic and clinical consequences of untreated epoetin alfa resistance include escalating epoetin alfa doses and the associated costs. Failure to deal with the underlying and potentially correctable causes of epoetin alfa resistance robs patients of the health benefits of maintaining their target hemoglobin and wastes health care dollars.

The identified causes of epoetin alfa resistance include medical conditions and deficiencies commonly seen in patients with chronic dialysis such as iron deficiency, blood loss, underdialysis, vitamin B_{12} and folic acid deficiency, infection, inflammation, aluminum toxicity, osteitis fibrosa cystica, and epoetin alfa noncompliance.[10-13] Other possible causes of epoetin alfa resistance include hemoglobinopathies, multiple myeloma, malnutrition, hemolysis, and pure red cell aplasia.

Before the project described in this paper, a physician, pharmacist, and nurse assessed anemia monthly in patients with chronic dialysis seen in the hemodialysis unit at St Paul's Hospital, Saskatoon, Saskatchewan, and adjusted epoetin alfa doses according to a protocol. However, epoetin alfa resistance was not systematically identified and managed.

The objective of the project described here was to develop and validate an algorithm to guide the investigation and management of suspected epoetin alfa resistance in patients on chronic dialysis. This report describes the experience of staff at the Renal Risk Reduction Centre at St Paul's Hospital with the algorithm from October 2000 to March 2001.

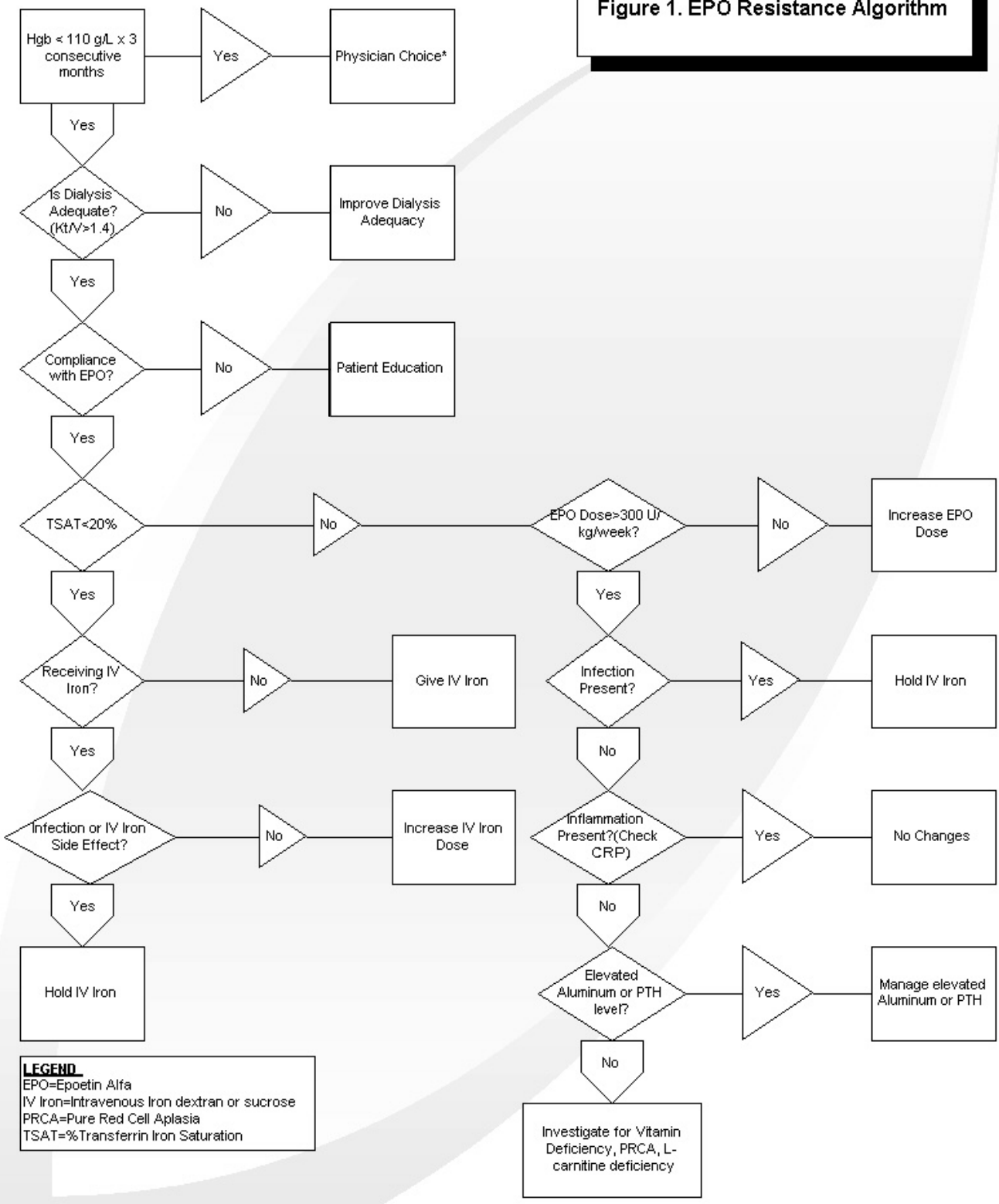
METHODS

After searching MEDLINE to identify common causes of epoetin alfa resistance, the authors from the Renal Risk Reduction Centre at St Paul's Hospital, Saskatoon, Saskatchewan, developed an algorithm to guide the investigation and management of suspected epoetin alfa resistance. After discussion with nurses and physicians in the renal unit, the algorithm was modified. The algorithm (Figure 1) was designed for use by physicians, pharmacists, and nurses involved in the management of patients on chronic dialysis.

For the purposes of the algorithm, epoetin alfa resistance was defined as the receipt of epoetin alfa doses of more than 300 IU kg^{-1} $week^{-1}$ SC[10], regardless of the hemoglobin concentration. Iron deficiency was defined as an iron saturation of less than 20% or a serum ferritin of less than 100 µg/L in the previous 3 months.[2] Inadequate dialysis was defined as a Kt/V of less than 1.4.[14] The Kt/V is a measure of dialysis adequacy, where K is the dialyzer clearance, t is the treatment time, and V is the volume of urea.[10] Infection and inflammation were defined as a current infectious or inflammatory disease such as active systemic lupus erythematosus, Wegener's granulomatosis, or pericarditis. Elevated aluminum and parathyroid hormone serum concentrations were defined as concentrations greater than 2300 nmol/L and 20 pmol/L, respectively.[15,16]

All patients seen in the hemodialysis clinic from October through December 2000 who had a hemoglobin concentration of less than 110 g/L for 3 consecutive months and who were taking any dose of epoetin alfa were identified. The algorithm was then used by a pharmacist and a physician to identify possible causes of anemia and to guide its management. Patient outcomes were tracked for 3 months after patients were enrolled in the study. Serum iron, total

Figure 1. EPO Resistance Algorithm



iron-binding capacity, and percent iron saturation were determined every 3 months from the time of enrolment in the study until the study's end in March 2001. Hemoglobin concentrations were assessed monthly, and serum vitamin B_{12} and folic acid concentrations were assessed in January 2001.

All data are presented as means standard deviation. A paired Student *t*-test was used to compare patient hemoglobin concentrations at baseline and at the end of the 3-month follow-up period. Statistical significance was defined as $p = 0.05$.

Table 1. Characteristics of 21 Patients Identified with a Hemoglobin Concentration Less Than 110 g/L for 3 Consecutive Months*

Characteristic	Value
Male/female (no.)	8/13
Mean epoetin alfa dose (IU kg^{-1} $week^{-1}$)	295 ± 165
Mean iron saturation (%)	18 ± 9
Mean dialyzer adequacy (*Kt/V*)	1.51 ± 0.31

K = dialyzer clearance, *t* = treatment time, *V* = volume of urea.
*Continuous data are presented as means ± standard deviation.

RESULTS

From October 1 to December 31, 2000, 212 patients were screened and 21 (10%) patients with a hemoglobin concentration less than 110 g/L for 3 consecutive months were identified (Table 1). All identified patients were receiving epoetin alfa, a multiple vitamin preparation (Dia-Vite, R&D Laboratories, Marina Del Rey, California), and iron supplementation. The majority (62%, 13/21) of patients were receiving intravenous iron dextran.

With the use of the algorithm, the 21 patients identified were divided into 5 groups: (i) those for whom correction of their anemia was not their physician's long-term goal (0%, 0/21 patients), (ii) those with dialysis inadequacy (24%, 5/21 patients), (iii) those who were noncompliant with their epoetin alfa regimen (0%, 0/21 patients), (iv) those with iron deficiency (48%, 10/21 patients), and (v) those with epoetin alfa resistance (38%, 8/21 patients). Many patients had more than one suspected cause of epoetin alfa nonresponse.

Suspected epoetin alfa resistance in 8 patients was caused by one of the following: chronic infection (tuberculosis, calciphylaxis infected lesions, chronic osteomyelytis, or fungal peritonitis), chronic inflammation (chronic Wegener's granulomatosis, pericarditis, systemic lupus erythematosus, or calciphylaxis), or hyperparathyroidism.

In most cases, a single intervention aimed at correcting anemia was made, and its effect on hemoglobin concentrations was evaluated for at least 1 month. However, patients receiving inadequate dialysis often had their dialysis regimen adjusted, coincident with another intervention aimed at improving their hemoglobin concentrations. Outcomes could not be determined for 5 of the 21 patients identified: 3 patients died, 1 patient received a kidney transplant, and 1 patient switched to peritoneal dialysis during the follow-up period.

Outcomes for the 16 patients who completed the follow-up period are listed in Table 2. Mean hemoglobin concentrations improved from baseline to the end of the follow-up period from 92.8 ± 11.0 to 106.9 ± 14.7 g/L ($p = 0.0009$).

The majority (11/16) of patients achieved a hemoglobin concentration greater than 110 g/L within the 3-month follow-up period. Nine of these 11 patients achieved a hemoglobin concentration of 110 g/L 1 month after they were identified. Both patients with inflammation (Wegener's granulomatosis, calciphylaxis) were receiving active treatment before the study period and achieved their target hemoglobin without further intervention. Similarly, the patient with hyperparathyroidism was receiving treatment with intravenous calcitriol before the study period and achieved the target hemoglobin without additional treatment. Two further patients achieved the target hemoglobin during the follow-up period: one after problems with underdialysis, acute and chronic infection, and a low epoetin alfa dose were dealt with; the other after recovering from bleeding in the upper gastrointestinal tract.

The remaining 5 of the 16 patients did not achieve their target hemoglobin, despite increases in their epoetin alfa doses and administration of intravenous iron. The suspected reasons for their not achieving their target hemoglobin were chronic underdialysis (the patient's choice), persistent pericarditis, active systemic lupus erythematosus, a low epoetin alfa dose, and an unknown cause. In the case of the patient who had epoetin alfa resistance of unknown cause, a hematologist recommended additional investigations (haptoglobin concentration, reticulocyte count, parvovirus serology) and an increase of the epoetin alfa dose beyond 300 IU kg^{-1} $week^{-1}$. No other patient had the epoetin alfa dose increased beyond 300 IU kg^{-1} $week^{-1}$.

DISCUSSION

The algorithm developed to guide the investigation and management of chronic dialysis patients with

Table 2. Outcomes for 16 Patients Followed for 3 Months

Pt No.	Time	Date (mo/y)	Hgb (g/L)	Cause(s) of EPO resistance	Action	Goal Hgb Achieved
1	Baseline	11/00	109	Underdialysis	Change dialysis filter	
	Follow-up	12/00	125		No change	Yes
2	Baseline	10/00	88	?Hyperparathyroidism	✔ PTH/AL	
	Follow-up	11/00	113	Aluminum toxicity	No change	Yes
3	Baseline	12/00	88	Fe deficiency	IV iron	
	Follow-up	01/01	128		No change	Yes
4	Baseline	10/00	98	Tuberculosis	No change	No
	Follow-up	11/00	72	EPO dose low	Inc EPO dose	No
		12/00	78	Underdialysis	Inc dialysis time	No
		01/01	84	Infection	No change	No
		02/01	98	EPO dose low	Inc EPO dose	No
		03/01	112		No change	Yes
5	Baseline	12/00	101	Fe deficiency	IV iron	
	Follow-up	01/01	112		No change	Yes
6	Baseline	10/00	101	Wegener's granulomatosis	No change	
	Follow-up	11/00	115		No change	Yes
7	Baseline	12/00	92	EPO dose low	Inc EPO dose	
	Follow-up	01/01	93	Fe deficiency; EPO dose low	Inc EPO; IV iron dose	No
		02/01	96	EPO dose low	Inc EPO dose	No
		03/01	109	EPO dose low	Inc EPO dose	No
8	Baseline	10/00	89	EPO dose low	Inc EPO dose	
	Follow-up	11/00	112		No change	Yes
9	Baseline	11/00	101	EPO dose low; underdialysis	Inc EPO dose; change dialysis filter; time	
	Follow-up	12/00	110		No change	Yes
10	Baseline	11/00	80	Fe deficiency	No change	No
	Follow-up	12/00	89	Fe deficiency	IV iron	No
		01/01	58	Upper GI bleeding	Blood transfusion	No
		02/01	110		No change	Yes
11	Baseline	10/00	92	Fe deficiency	Inc IV iron dose	
	Follow-up	11/00	95	Fe deficiency	No changes	No
		12/01	102	Pericarditis	No changes	No
		01/01	99	Pericarditis	No changes	No
		02/01	76	Pericarditis	No changes	No
		03/01	70	EPO dose low	Inc EPO dose	No
12	Baseline	10/00	99	Fe deficiency; underdialysis	Inc IV iron dose	No
	Follow-up	11/00	89	Underdialysis	No change	No
		12/00	93	EPO dose low; underdialysis	Inc EPO dose	No
		01/01	97	EPO dose low; underdialysis	Inc EPO dose	
		02/01	ND			
		03/01	100	EPO dose low; underdialysis	Inc EPO dose	No
13	Baseline	12/00	68	Fe deficiency	Inc EPO dose	No
	Follow-up	01/01	75	EPO dose low	IV iron held	No
		02/01	93	Active SLE	SLE treated	No
		03/01	93	Active SLE	SLE treated	No
14	Baseline	10/00	102	Calciphylaxis	No change	
	Follow-up	11/00	111		No change	Yes
15	Baseline	10/00	76	Underdialysis	Inc dialysis treatment duration	No
	Follow-up	11/00	78	Underdialysis*; Fe deficiency; EPO dose low	Inc EPO dose; ✔ ferritin; iron saturation	No
		12/00	80	Underdialysis*; ?bleeding	Inc Fe, OB stool	No
		01/01	87	Unknown	No changes	No
		02/01	82	Unknown	✔ Haptoglobin; reticulocyte count; inc EPO dose	No
		03/01	83	Unknown	✔ Parvovirus serology; inc EPO dose	No
16	Baseline	12/00	101	EPO dose low	Inc EPO dose	
	Follow-up	01/01	114		No change	Yes

Pt No. = patient number, Hgb = hemoglobin concentration, EPO = epoetin alfa, ? = query,
✔ PTH/AL = parathyroid hormone and aluminum serum levels checked, Fe deficiency = iron deficiency, IV iron = intravenous iron dextran, Inc = increase, GI = gastrointestinal tract, ND = not done, SLE = systemic lupus erythematosus, ✔ = check, OB stool = stool for occult blood.
*Patient was underdialyzed because the hemodialysis catheter was functioning poorly.

suspected epoetin alfa resistance was successfully used to manage 16 patients who did not achieve a target hemoglobin of 110 g/L with epoetin alfa for 3 consecutive months. With the use of the algorithm, these patients were managed in 1 of 5 ways. Patients with iron deficiency received intravenous iron or an increase in the oral iron dose. Dialysis efficiency was improved in patients receiving inadequate dialysis. Patients with a subcutaneous epoetin alfa dose greater than 300 IU kg^{-1} $week^{-1}$ were investigated for possible causes of epoetin alfa resistance, such as hyperparathyroidism, aluminum toxicity, infection, or inflammation. Patients with a subcutaneous epoetin alfa dose less than 300 units kg^{-1} $week^{-1}$ were eligible for an increased dose with a standard epoetin alfa–dosing protocol.

The most commonly identified causes of epoetin alfa nonresponse included iron deficiency, a low epoetin alfa dose, and epoetin alfa resistance caused by hyperparathyroidism, chronic infection, inflammation, or dialysis inadequacy. Many patients had more than one suspected cause of nonresponse.

Although the algorithm was useful for guiding the investigation and management of the patients in the project, the following changes would improve the usefulness of the algorithm for patients who are nonresponsive to epoetin alfa. First, the distinction between epoetin alfa nonresponse and resistance is arbitrary. The KDOQI guidelines[10] do not consider iron deficiency a cause of epoetin alfa resistance and imply that patients should receive subcutaneous epoetin alfa doses greater than 300 IU kg^{-1} $week^{-1}$ for 4 to 6 months before other causes of resistance are investigated. Since iron deficiency seems to affect response at any epoetin alfa dose, this philosophy seems inappropriate.[11-13,17,18] Second, since iron deficiency was the most common cause of epoetin alfa nonresponse in the patients in this project, its prominence in the algorithm should be increased. Finally, although dialysis inadequacy was frequently identified in the study patients, its importance in the algorithm should be reduced since it can be dealt with easily at the same time as other suspected causes of epoetin alfa nonresponse.

Although the majority (62%) of patients were receiving intravenous iron, the most commonly identified cause of nonresponse to epoetin alfa was iron deficiency. The findings of this study concur with those of other studies[10-12] that the most common cause of epoetin alfa nonresponse or resistance is iron deficiency. Since the KDOQI definition of epoetin alfa resistance was used, iron deficiency was not categorized as resistance. Iron deficiency in patients on chronic hemodialysis is characterized by ferritin concentrations less than 100 µg/L or transferrin iron saturation of less than 20%.[10,19] Ferritin is also an acute-phase reactant and its concentration is elevated in patients with infection and inflammation. Therefore, under these circumstances, the use of ferritin to evaluate iron stores may be misleading. Iron supplementation is required in up to 90% of those treated with epoetin alfa.[20] Use of oral iron salts, such as ferrous sulfate, in doses of 200 mg/day of elemental iron is recommended for initial therapy. For many patients, intravenous iron supplementation may be required.[17] Iron, total iron-binding capacity, and iron saturation were assessed every 3 months in this study, and intravenous iron dextran or sucrose was actively prescribed for patients who did not respond to oral iron salts. Despite this, it seemed that many of the patients in the current study were still not receiving inadequate iron supplementation. This suggests that patients may rapidly develop iron deficiency, either because of inadequate supplementation or increased demand from erythropoiesis. More frequent assessment and evaluation of iron stores are likely required to identify and manage iron deficiency in these patients.

The benefits of intravenous iron include optimization of hemoglobin concentrations, reductions in epoetin alfa dose, and subsequent cost savings.[21] However, the use of intravenous iron includes the risk of adverse effects such as hypotension, flushing, dizziness, fever, back pain, headache, myalgia, arthralgia, lymphadenopathy, iron overload, infection, and, rarely, anaphylaxis.[18,22] The possible link between the use of intravenous iron and infection remains controversial. It has not been systematically examined.[23] A retrospective review of United States Medicare claims from approximately 20 000 hemodialysis patients showed that patients receiving more than 17 vials (1700 mg) of iron dextran during a 6-month period had a significantly higher risk of death because of infection than those who did not receive iron.[23-25] At the hemodialysis unit at St Paul's Hospital in Saskatoon, Saskatchewan, patients are frequently given an iron-loading dose of 1 g, plus 5 monthly maintenance doses of 100 to 200 mg or maintenance doses greater than 300 to 400 mg monthly. These patients could be at risk for exacerbation of infection. Iron is believed to exacerbate infection by providing a substrate for bacterial growth and by inhibiting the optimal function of leukocytes.[26] Until further evidence is available, it would be prudent to avoid giving intravenous iron to patients with chronic infections, such as osteomyelitis or tuberculosis, when recovery is expected to take several months.

Localized or systemic infection and inflammation also indirectly cause epoetin alfa resistance by reducing iron delivery from reticuloendothelial cells. Reticuloendothelial blockade is likely caused by increased circulating levels of acute-phase reactants and cytokines such as C-reactive protein, tumour necrosis alfa, ferritin, and interleukins.[11,27,28] Inflammatory and infectious disease processes that elicit an acute-phase response will result in reticuloendothelial block and decrease response to epoetin alfa. Hypoalbuminemia, a marker of poor nutritional status, is also a marker of the acute-phase response. In a study by Gunnell and others,[29] hypoalbuminemia and elevated C-reactive protein were the most important predictors of epoetin alfa resistance in well-dialysed patients who were iron-replete. Until chronic infectious or inflammatory processes resolve, patients will exhibit epoetin alfa resistance. Therefore, for these patients, increasing the epoetin alfa dose is not recommended.

Hyperparathyroidism also seems to play a role in epoetin alfa resistance. Serum erythropoietin levels increase and the epoetin alfa dose decreases after subtotal parathyroidectomy in hemodialysis patients with severe secondary hyperparathyroidism.[30,31] Epoetin alfa resistance in patients with secondary hyperparathyroidism seems to be related to bone marrow fibrosis.[32] Although no correlation between epoetin alfa requirements and parathyroid hormone concentrations seems to exist, a correlation between the osseous effects of excess parathyroid hormone and epoetin alfa requirements has been demonstrated. Further, parathyroid hormone suppression with intravenous calcitriol results in improved response to epoetin alfa among patients with hyperparathyroidism.[33]

Aluminum intoxication has been long recognized as an independent cause of a microcytic hypochromic anemia in patients with end-stage renal disease who require dialysis.[34] Aluminum seems to interfere with heme synthesis enzymes, resulting in an accumulation of protoporphyrin and interference in iron distribution and metabolism. Not surprisingly, aluminum overload markedly reduces the response to epoetin alfa.[35-38] Treatment of aluminum overload with deferoxamine has resulted in improvements in hematocrit.[32] Aluminum intoxication is rare because most hemodialysis units deionize the dialysis water used during treatment, thereby eliminating a previously important source of aluminum.[34] Currently, the major causes of aluminum intoxication include the use of aluminum-containing phosphate binders. For patients with identified aluminum intoxication characterized by a serum aluminum level greater than 2300 nmol/L, discontinuation of aluminum-containing phosphate binders and substitution of a calcium-containing phosphate binder such as calcium carbonate or acetate or a noncalcium-containing nonaluminum-containing phosphate binder such as sevelamer is recommended.[15]

Several patients who were inadequately dialysed (*Kt/V* less than 1.4) were identified in the current study. In one study,[39] inadequate dialysis, characterized by a urea reduction ratio of less than 65%, was associated with a poor response to epoetin alfa. Increasing the intensity of dialysis in underdialyzed patients resulted in an increase in the hematocrit.[39] Uremic toxins are postulated to interfere with erythropoiesis, resulting in epoetin alfa resistance in underdialyzed patients with end-stage renal disease.[39] Of 4 underdialyzed patients who were evaluable in the current study, 2 patients achieved their target hemoglobin when the intensity of dialysis was increased.

Finally, other reported causes of epoetin alfa resistance include L-carnitine deficiency, pure red cell aplasia, vitamin deficiency, and poor absorption from the subcutaneous injection in obese patients.[40-44] L-Carnitine is a natural carrier of fatty acids from the cellular cytoplasm to the mitochondrial matrix, where fatty acids undergo oxidation.[40] Hemodialysis patients usually present with a severe carnitine deficiency resulting from inadequate intake, impaired synthesis, and loss of L-carnitine during dialysis. Supplementation with intravenous L-carnitine reduces epoetin alfa dosage by enhancing the stimulatory effects of erythropoietin on the production of erythroid precursors. At the renal clinic where the study was done, patients whose clinical symptoms were solely a result of L-carnitine deficiency were difficult to identify. Therefore, L-carnitine deficiency may be a diagnosis made after the exclusion of other possible causes of epoetin alfa resistance.

Vitamin B_{12} and folic acid deficiency is common among patients with chronic renal disease who do not receive vitamin supplementation.[42,43] Therefore, some reports[42-44] describe it as an important cause of resistance. Because all the patients in the current study received vitamin supplementation, vitamin deficiency was rarely identified as a cause of epoetin alfa resistance. Therefore, its prominence in the algorithm was minimized.

Also, during home dialysis or hemodialysis for patients who self-administer epoetin alfa, noncompliance may be a cause of nonresponse to epoetin alfa. These patients should receive education that stresses the

importance of compliance. Hemodialysis unit nurses in the current study administered all epoetin alfa to patients during their treatments. Therefore, noncompliance with epoetin alfa was not identified as a cause of nonresponse.

Finally, correction of anemia may not be a possible or suitable goal for patients who receive palliative dialysis or who are noncompliant with dialysis treatments. For this reason, the algorithm developed allows the clinician to choose not to correct the anemia.

Epoetin alfa resistance or nonresponse is a complex issue. The algorithm developed for the current study offers a practical tool for the identification and management of dialysis patients not responding to epoetin alfa. This tool allows systematic identification of epoetin alfa nonresponse and correction of underlying causes.

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