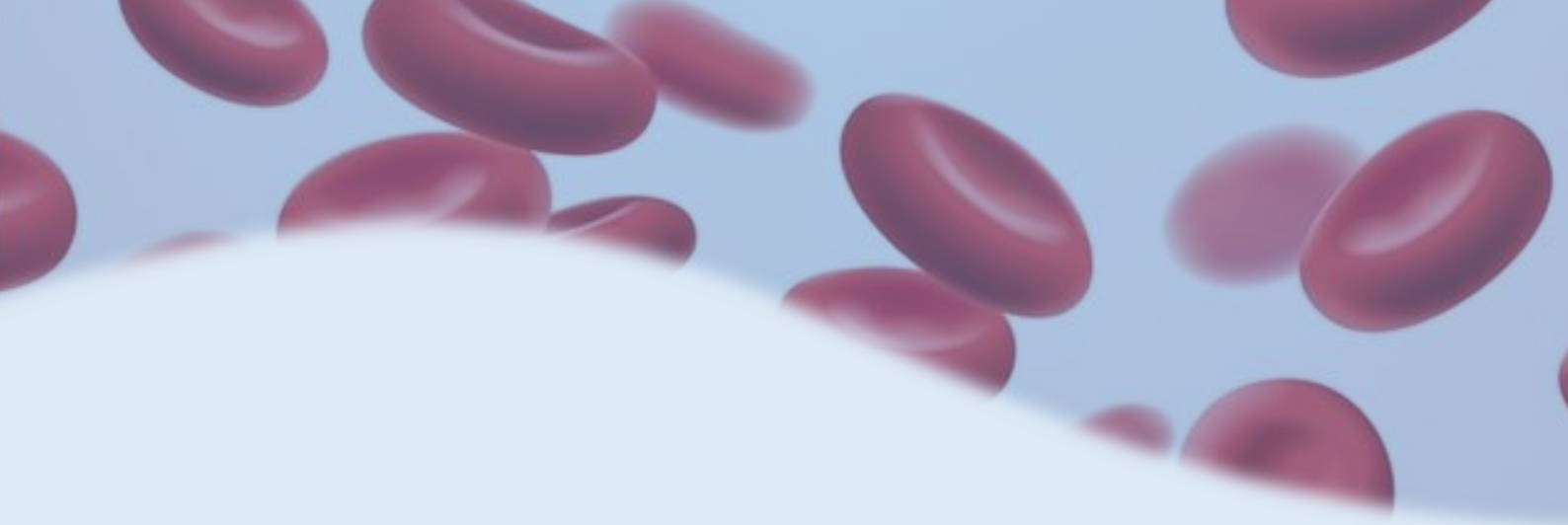


Practical Applications of Human Recombinant Erythropoietin (rhEPO) in Clinical Practice

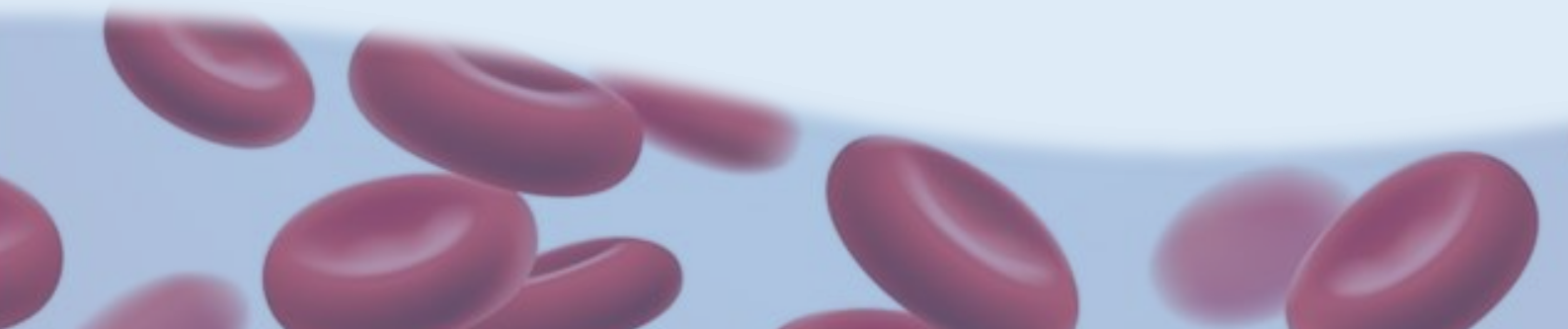


Table of Content

Background and Objective of the Survey

Human recombinant erythropoietin (rhEPO) has significant clinical applications, primarily in managing anemia. In chronic kidney disease (CKD), rhEPO corrects anemia by compensating for the kidneys' inability to produce sufficient erythropoietin. It is also crucial in treating anemia in cancer patients undergoing chemotherapy, improving their quality of life by reducing fatigue. Preoperatively, rhEPO is used to increase red blood cell mass, minimizing the need for blood transfusions during surgery. Additionally, it benefits HIV patients and premature infants who often suffer from anemia. In myelodysplastic syndromes (MDS), rhEPO can reduce transfusion dependence and alleviate symptoms. However, the use of rhEPO requires careful monitoring to prevent adverse effects such as hypertension and thromboembolic events. Regular assessments of hemoglobin levels, blood pressure, and iron status are essential for safe and effective treatment. Overall, rhEPO's ability to stimulate red blood cell production makes it a vital tool in anemia management across various conditions.

The objective of the survey is:

To evaluate the understand the practical applications of human recombinant erythropoietin (rhEPO) in clinical practice

Methodology of the Survey

A survey was conducted to evaluate the understand the practical applications of human recombinant erythropoietin (rhEPO) in clinical practice. A total of 80 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Historical Perspective
- Recombinant Human Erythropoietin
- Mechanism of Action
- Administration of Rhuepo
- Clinical Application of Rhuepo
- Anaemia Associated with Chronic Renal Disease
- Route of Erythropoiesis Stimulating Agents (ESA)
- Route of Administration and Stage of CKD (Non-Dialysis Dependent and Patients on Peritoneal Dialysis vs Haemodialysis Patients)
- Convenience of Drug Administration

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

The human body generates 2.5 million new red blood cells (RBCs) per second from the bone marrow to replenish the continuous removal of effete RBCs. The production of RBCs (erythropoiesis) is controlled by an intricate interaction between various humoral factors and cytokines. A specific cytokine, a sialoglycoprotein known as erythropoietin, which acts directly on certain RBC progenitors and precursors in the bone marrow, controls the proliferation, differentiation, and maturation of RBCs. The expression of erythropoietin is markedly increased in kidneys during hypoxic state, a condition mediated by the transcription factor HIF-1. The ultimate effect is to increase erythropoiesis in an attempt to maintain oxygen delivery to vital organs. This article provides an overview of erythropoietin on both historical and scientific aspects, followed by a discussion of its current and potential applications in clinical medicine.

Historical Perspective[1]

From observation to discovery

A positive correlation of hypoxia and anaemia with erythrocytosis has been noticed through clinical observations and experimentations since the late 19th century (table 1). Nevertheless, the purification of erythropoietin has been difficult because of technical limitations, heterogeneity of target cell population, and insufficient quantity of erythropoietin available for further analysis. A major breakthrough occurred in 1977 when Miyake and coworkers successfully purified and characterised human erythropoietin from urine of patients with aplastic anaemia. In 1985, two groups of investigators independently cloned the human erythropoietin gene with the identification of the corresponding nucleotide sequences.

Table 1 Historical perspective of erythropoietin (EPO), adapted from Jelkmann[1]

Contributors	Contributions	Comment
Bert (1882) Viault (1890) Miescher (1890)	Observation of increased RBC count at high altitude	A direct relationship of hypoxia to RBC count was proposed
Carnot and Deflandre (1906)	Experiment on injected blood from anaemic rabbits to donor rabbits causing a 20%–40% increased RBC in blood	Suggested a humoral factor "haemopoietine" to control RBC production
Muller (1912) Sandor (1932) Krumdieck (1943)	Experiment on injected blood from hypoxic rabbits to donor rabbits causing an increased RBC in blood	A direct relationship of hypoxia to RBC count demonstrated
Bonsdorff and Jalavisto (1948)	Experiment on injected blood from hypoxic animals to untreated animals causing a raised RBC production	"Erythropoietin" was introduced to support the presence and the transferability of the humoral factor
Reissmann (1950) Ruhenstroth-Bauer (1950)	Increased RBC production on parabiotic animals when hypoxia and anaemia was introduced in one of them	A direct evidence of the presence of EPO to cause an increase in RBC in hypoxia/anaemia
Erslev (1953)	Repeated infusing plasma from severely anaemic rabbits to donor rabbits causing increased packed cell volume/reticulocyte count	Predicted the therapeutic potential of EPO if purified
Hodgson and Toha (1954)	EPO activity isolated in urine and plasma of anaemic rabbits	First to demonstrate EPO activity in urine
Stohlman *et al* (1954) Schmid and Gilbersten (1955)	Observations of RBC hyperplasia in bone marrow in patients with patent ductus arteriosus	Suggested hypoxia of lower part of body and increased erythropoiesis
Jacobson *et al* (1957)	No increase in RBC in nephrectomised animals	First to support EPO production of renal origin
Kuratowsha *et al* (1961) Fisher and Birdwell (1961)	Detection of EPO activity in isolated perfused kidney	Confirmed kidney as a source of EPO production
Fischer *et al* (1965) Frenkel *et al* (1968)	Localisation of EPO production to renal glomeruli	Suggested the regional secretion of EPO in kidney
Katz *et al* (1968) Fried (1972)	Detection of EPO activity in liver	Confirmed liver as another source of EPO production
Essers *et al* (1974)	Suggested liver being insufficient to replace kidney for EPO production	Supported kidney as the main source of EPO production
Miyake *et al* (1977)	Purification of EPO from urine in patients with aplastic anaemia	First to isolate and characterise EPO
Anagnostone *et al* (1977) Van Stone and Max (1979) Eschbach *et al* (1984)	EPO on animals with anaemia of renal failure	Demonstrated the effectiveness of EPO to correct anaemia
Jacobs *et al* (1985)	Cloning of EPO gene via "reverse genetics"	Paved the way for industrial manufacturing of recombinant EPO
Lin *et al* (1985)		Allowed sufficient quantity of EPO for clinical use

From discovery to clinical practice

Before the availability of recombinant human erythropoietin (RHuEPO), the only treatment for patients with anaemia of chronic renal failure was blood transfusion. Unfortunately, blood transfusion had to be given regularly so as to maintain the haemoglobin level. Furthermore, various transfusion related problems, in particular iron overload, significantly compromised the management and outcome of renal patients. Based on the promising results on animal models, erythropoietin was considered a prime candidate as replacement therapy. As soon as RHuEPO was made available for human trial, a series of clinical studies were promptly conducted to assess its effectiveness in correcting anaemia of chronic renal disease. The initial results demonstrated that RHuEPO could restore the packed cell volume, abrogate the necessity of regular blood transfusion in patients requiring dialysis, and improve the overall wellbeing. The results of these trials were so impressive that RHuEPO was granted a licence as a

therapeutic agent in 1988 for patients with anaemia of chronic renal failure, only three years after its discovery.

Recombinant Human Erythropoietin[1]

Structural and biological characteristics

Erythropoietin in blood is mainly of renal origin, with a small amount derived from the liver. The human erythropoietin gene is situated at chromosome 7q11-22, consisting of five exons and four introns, which produces a post-transcriptional single polypeptide containing 193 amino acids. During the post-translational modification, glycosylation occurs with the addition of three N-linked (at Asn-24, Asn-38 and Asn-83) and one O-linked (at Ser-126) acidic oligosaccharides, the formation of two disulphide bonds at Cys-7 to Cys-161 and at Cys-29 to Cys-33, concomitant with the removal of the 27 amino acid hydrophobic secretory sequence. The Arg-166 at the COOH terminal is believed to be cleaved before the release of erythropoietin into the circulation, with the primary structure of a mature erythropoietin (and hence RHuEPO) containing 165 amino acids (fig 1). The molecular mass of the polypeptide backbone and the glycosylated form of erythropoietin is estimated to be 18 kDa and 30 kDa respectively. Circular dichroism spectral analysis has proposed that its secondary structure contains 50% of α-helix moiety, with spatial arrangement of two α-helical pairs running antiparallel similar to that of growth hormone. The glycosylated (or sugar) moiety of erythropoietin has an important role in terms of biosynthesis, tertiary structure of the molecule, and in vivo biological activity. The N-glycosylated moiety of RHuEPO has three main functional units: the main core, the branched portion and the terminal component, with each unit having a specific role. The function of the O-glycosylated unit, a component constituting about 3% of the total mass of RHuEPO, remains to be defined. There are currently four different RHuEPOs: alpha, beta, delta, and omega. However, only EPO-alpha and EPO-beta are commercially available in the UK at the moment. Although these RHuEPOs act on the same erythropoietin receptor, there are some variations on the degree of glycosylation which lead to the differences in the pharmacokinetics and pharmacodynamics among the RhuEPOs.

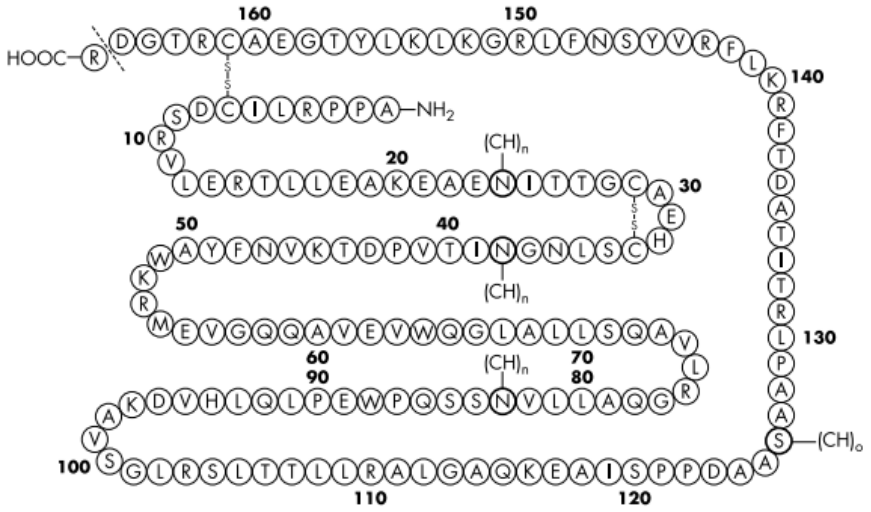


Figure 1 Primary structure of erythropoietin (hence RHuEPO). $(CH)_n$, *N*-linked glycosylation site at aspartyl residues 24, 38, 83; $(CH)_o$, *O*-linked glycosylation site at seryl residue 126. **NB**: The ARG-166 at the carboxyl terminal is removed before erythropoietin is released into the circulation.

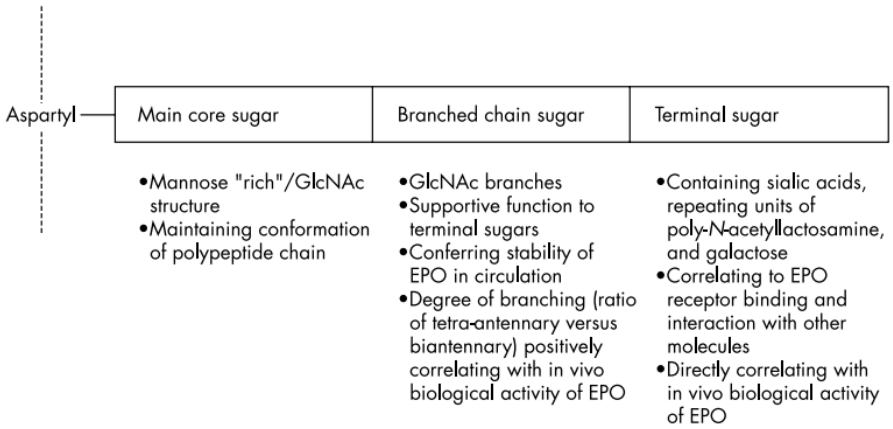


Figure 2 Outline of the functional units from *N*-glycosylation moiety of erythropoietin (EPO).

Modifications of RHuEPO

As the N-glycosylation confers the biological activity of RHuEPO, an increase in the number of glycosylation sites may enhance its activity. A hyperglycosylated RHuEPO, known as NESP (novel erythropoiesis stimulating protein; Darbepoetinalpha) has recently been introduced. By using a process called “site mutagenesis”, the polypeptide backbone of the RHuEPO is modified, leading to the creation of five N-glycosylation sites (compared with three in RHuEPO).

Compared with the RHuEPOs, NESP has a higher negative charge and a threefold longer half life. It requires a less frequent dosing schedule and produces a similar clinical outcome and safety profile as RHuEPOs in treating anaemia of chronic renal disease and of malignancy. The applicability of NESP in other clinical conditions is currently being evaluated.

Another strategy to enhance the biological activity of RHuEPO is to provide a "protective vehicle" so as to decrease the rate of elimination, thus prolonging the half life of RHuEPO. Methods such as microencapsulation and pegylation to RHuEPO are currently being assessed.

Mechanism of action[1]

Erythropoietin is essential for the proliferation, differentiation, and maturation of RBCs in bone marrow. Moreover, erythropoietin is critical for the survival of RBC progenitors in bone marrow and may also have immunomodulatory activity. Erythropoietin functions by binding to the erythropoietin receptor: a 72–78 kDa glycosylated and phosphorylated transmembrane polypeptide. The erythropoietin receptor is a member of the superfamily of cytokine receptors. The number of erythropoietin receptors varies during RBC differentiation, with its peak presentation at the colony forming unit-erythroid/proerythroblastic stage and the level being undetectable at the reticulocytes. The binding of erythropoietin to its receptor results in homodimerisation of the receptor, followed by activation of several signal transduction pathways: JAK2/STAT5 system, G-protein (RAS), calcium channel, and kinases (fig 3).

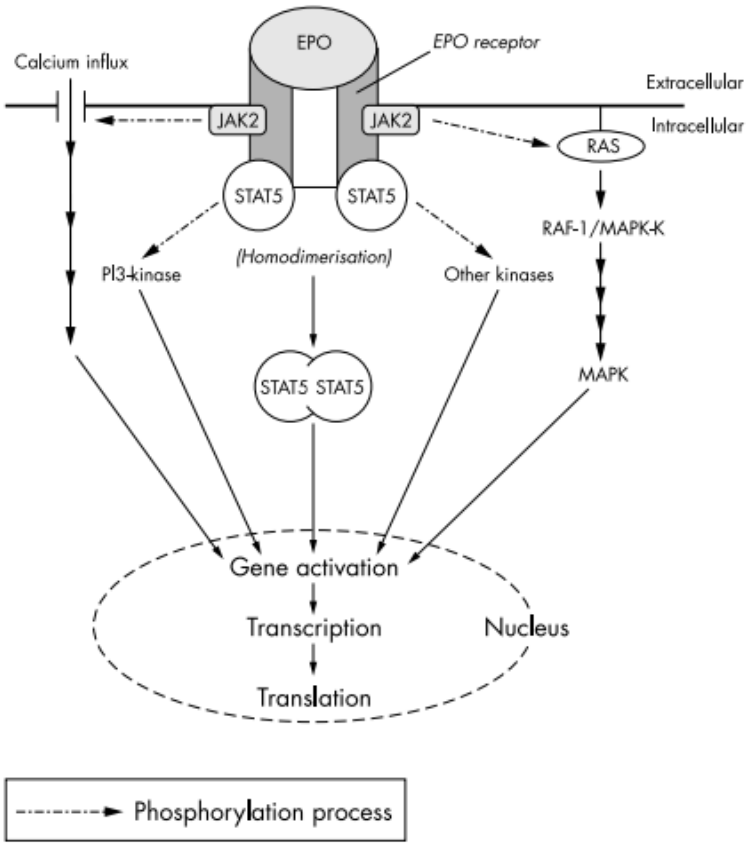


Figure 3 Simplistic view of the main signal transduction pathways activated by the erythropoietin (EPO) receptor.

Administration Of Rhuepo[1]

Route of administration

Both intravenous and subcutaneous administrations are commonly used to deliver RHuEPO to renal patients. Clinical studies have demonstrated that the subcutaneous route offers a few advantages over intravenous administration. For instance, subcutaneous administration is more convenient as it does not require any venous access. When compared with the intravenous route, subcutaneous RHuEPO administration significantly prolongs the increase of serum erythropoietin, thus sustaining the stimulation of erythropoiesis. Furthermore, up to 30% reduction in total weekly RHuEPO dosage on haemodialysis patients could be achieved to maintain the same haemoglobin level when switching intravenous to subcutaneous administration. Intraperitoneal administration of RHuEPO could be an alternative for the subcutaneous route but it is mainly applicable to renal patients receiving peritoneal dialysis. A larger dose of RHuEPO may be required to maintain the same haemoglobin level if RHuEPO has to be applied intraperitoneally.

As there is an increasing concern of pure red cell aplasia associated with subcutaneous EPO-alpha administration to renal patients, the Department of Health in UK recommends a change in the route of EPO-alpha administration from subcutaneous to intravenous. However, it remains uncertain whether similar measure will be applied to the other recombinant erythropoietins.

Outside the uraemic setting, both intravenous and subcutaneous RHuEPO have been employed but the subcutaneous route was used in the majority of the studies. However, there have been no studies to compare the efficacy of these routes.

Frequency of administration

Both intravenous and subcutaneous RHuEPO can be given from once daily to thrice, twice and once weekly in renal patients, depending on the clinical status of the patients. Similar differences in the frequency of RHuEPO administration have been applied in various non-uraemic conditions.

Clinical Application of Rhuepo[1]

RHuEPO has revolutionised the treatment of patients with anaemia of chronic renal failure. Moreover, RHuEPO has been shown to be effective in correcting anaemia associated with various non-uraemic conditions (box 1).

Table 2: **Clinical applications of RHuEPO**

- Replacement therapy (low endogenous erythropoietin level) in anaemia associated with:

(A) Chronic renal failure.
(B) Malignancy.
(C) Prematurity.
(D) HIV infection.

- Supportive therapy (to maintain/accelerate erythropoiesis) in:

(A) Post-chemotherapy/post-radiotherapy.
(B) Post-transplantation.

- Augmentative therapy (increase haemoglobin above physiological level) in:

(A) Surgery.
(B) Situations where blood transfusion is refused/disallowed.
(C) Sport (potential abuse by athletes).

- To enhance autologous transfusion so as to maintain haemoglobin perioperatively.
- Other potential therapeutic applications:

(A) Anaemia associated with—autoimmune diseases, acute haemolysis, haemoglobinopathy.
(B) Acute renal failure.
(C) Critically ill patients.
(D) Neuroprotection.
(E) Congestive cardiac failure.

Anaemia associated with chronic renal disease[1]

Chronic renal failure on maintenance dialysis

Patients with chronic renal failure have subnormal endogenous erythropoietin production. Clinical studies have shown that RHuEPO therapy corrects the anaemia of chronic renal failure, avoids blood transfusions and improves quality of life. Furthermore, it optimises a patient's haemodynamic status thus minimising the risk of progression to left ventricular hypertrophy

and its associated mortality. Furthermore, it leads to an improvement of physical performance and cognitive function.

Patients at pre-dialysis stage

A review published in 1995 suggested that pre-dialysis patients (and those with failing renal allografts) would gain no benefit from RHuEPO therapy if glomerular filtration rate was less than 15 ml/min but there would be a risk of accelerating to end stage renal failure. However, recent clinical studies have failed to confirm these negative effects of RHuEPO. In fact, a meta-analysis on published data involving 12 randomised studies with more than 200 pre-dialysis patients during the period 1980–2001 has shown that early treatment with RHuEPO corrected anaemia, avoided blood transfusion, and improved the quality of life and exercise capacity. Although there was an increase in the requirement for antihypertensive therapy, no statistically significant increase in adverse events was otherwise found. There was also no evidence to suggest that RHuEPO therapy hastened a deterioration of renal function, though the authors conceded that the duration of RHuEPO therapy in most of the trials might not be long enough to confirm the benefit. Early application of RHuEPO has been shown to reduce the risk of cardiovascular events and the associated mortality. The addition of intravenous iron may decrease the dosage requirement of RHuEPO and could provide an additive and rapid effect in the correction of renal anaemia during the pre-dialysis period.

Patients with renal transplant

Unfortunately, there are insufficient clinical data to discuss in details the use of RHuEPO in the transplant setting. The avoidance of pre-transplant blood transfusion may impair the success of graft survival in patients receiving a cadaveric transplant, according to collaborative transplant studies. Furthermore, there are concerns that an increase in packed cell volume during renal transplant may predispose the patient to develop graft thrombosis and delayed graft function. Muirhead reviewed the current data and highlighted several issues. Firstly, there was no convincing evidence of delayed graft function or graft thrombosis in patients previously treated with RHuEPO. Secondly, the use of RHuEPO might reduce allosensitisation as a result of random blood transfusion while allowing the benefits of graft survival from deliberate transfusion. Thirdly, the correction of posttransplant anaemia was enhanced and hastened by RHuEPO therapy. Fourthly, the effect of RHuEPO was minimal during an acute episode of graft rejection but its benefit resumed once successful treatment of the rejection episode had

been achieved. Finally, despite the use of immunosuppressants, patients with failing grafts had a similar response to RHuEPO compared with those on dialysis. A recent study in Sweden has shown that pre-transplant correction of haemoglobin reduced the necessity of postoperative blood transfusion with no evidence of worsening the transplant outcome.

Route of erythropoiesis stimulating agents (ESA) [2]

The major factors that govern the route of ESA administration include the patient's stage of CKD, efficacy considerations, the type of ESA used, dosing frequency, convenience, healthcare costs, and drug safety and tolerability. This literature review aims to discuss the existing, relevant literature for these factors with respect to the route of ESA administration and to define areas that need further exploration.

Dosing Frequency

Numerous studies and trials have documented evidence strongly suggestive of the advantages that the SC route of erythropoietin administration has, in terms of requiring a lower dose and frequency of administration, over the IV route (see Table 3)**.**

Table 3. **A summary of studies comparing dosing frequency between intravenous and subcutaneous routes of administration of erythropoietin**

HD: Haemodialysis, SC: Subcutaneous, IV: Intravenous, Hb: Haemoglobin, r-HuEPO: Recombinant Human Erythropoietin, ESRD: End-stage Renal Disease.

Serial Number	Author/Year	Study Design	Population	Relevant Conclusive Points
1	Muirhead et al. / 1992	Clinical Trial	128 adult HD patients selected from five dialysis centers, 45 patients withdrew due to various reasons. 45	Mean dose at stabilization of Hb levels, time to achieve target Hb levels and time to stabilization of

			patients were in the subcutaneous group (SC) and 38 in the intravenous (IV) group.	Hb levels of rHuEPO were all significantly lower in the SC compared to the IV group.
2	Wright et al. / 2015	Comparative Study (retrospective cohort)	62,710 adult HD patients enrolled in the Centers for Medicare and Medicaid Services ESRD Clinical Performance Measures Project from 1997 to 2005 were treated with epoetin, of which 57,602 patients received IV and 5108 received SC epoetin.	IV epoetin doses were on average 25% higher than the SC dose for achieving equivalent haemoglobin responses in study patients. Adverse outcomes on follow-up were also found to be significantly more likely in HD patients receiving IV rather than SC epoetin.
3	Vercaigne et al. / 2005	Clinical Trial	98 adult HD patients already on maintenance SC epoetin therapy enrolled into study and all patients were shifted to IV epoetin simultaneously for the prospective study of anemia. 34 patients withdrew at different stages due to various reasons. 64 patients took part in study.	IV Epoetin requirements increased by 35%, on average, compared to previous SC dosage whilst also resulting in a significantly lower mean Hb level. Similarly at the end of the IV epoetin evaluation period, 52% patients needed more frequent dosing than at

				the time of SC to IV epoetin conversion.
4	Moist et al. / 2006	Comparative Study (prospective cohort)	414 adult HD patients participated in this study, which was essentially a wide-scale policy implementation for a change from the maintenance SC epoetin administration route to the IV route. All patients were shifted simultaneously to the IV route. 111 patients withdrew from the study due to various reasons.	The mean weekly, weight-adjusted dose of IV epoetin was found to be 20.2% higher, on average, than the baseline SC dosage. This was most pronounced at 6 and 12 months of follow-up. Patients receiving epoetin 3 times per week increased from 19.6% at baseline, with SC administration, to 79.5% at 12 months of IV epoetin.
5	Galliford et al. / 2005	Comparative Study (prospective cohort)	86 adult HD patients were studied on a monthly basis for 6 months before and after a change in the route of administration from SC epoetin-alfa to IV epoetin-alfa.	Hb levels fell significantly in the first two months after the switch from SC epoetin-alfa to IV epoetin-alfa administration. This effect was partially offset at 6 months by an increase of IV epoetin-alfa dose by 32% along with an increase in costs.

6	Steffensen et al. / 2011	Randomized Controlled Trial (Open, multicentre Crossover study)	145 adult HD patients, already on SC Epoetin, were randomized to one of two epoetin treatment groups. The groups either involved treatment with IV epoetin for 4 months followed by SC administration for 4 months or vice versa. Routine iron studies were carried out during study and supplemented as needed.	Provided that iron stores are optimal, there is no significant difference in mean Hb levels and mean EPO doses between IV and SC administration of epoetin-beta.
7	Parker et al. / 1997	Clinical Trial	44 adult chronic HD patients from a dialysis unit, already on IV Epogen (r-HuEPO, Epoetin-alfa), were selected for this study and subjected to an approved treatment protocol comprised of 3 phases with different routes and doses of Epogen administration. 27 patients completed the protocol over 22 months. 135 “control” subjects were matched during the protocol	The outcomes showed that most chronic, stable HD patients can maintain stable hematocrit and Hb concentrations at once weekly SC EPO doses that are one-third of the required weekly IV dose thereby lending support to its safety and efficacy. Patient safety, serum biochemistry, blood pressure and red blood cell indices were also monitored during the study, with no

			from another group of dialysis patients refusing to opt for SC r-HuEPO.	significant differences in any variable between the control and experimental group.

Drug Safety and Tolerability[2]

As with any other drug, recombinant Human EPO (r-HuEPO) or epoetin carries with it a certain set of side effects. While both IV and SC share some of these adverse effects, the extent and frequency differ between the two (see Table 4). Common to both routes include injection site pain sensation, the development of hypertension, arteriovenous fistulae thrombosis, an increased overall risk of thrombotic and cardiovascular as well as cerebrovascular events, hyperkalemia, depletion of iron stores, flu-like symptoms, a prolonged duration of dialysis and rarely, PRCA and seizures.

Table 4. **A summary of studies comparing erythropoietin safety profile and tolerance between intravenous and subcutaneous administration**

HD: Haemodialysis, SC: Subcutaneous, IV: Intravenous, Hb: Haemoglobin, rHuEPO: Recombinant Human Erythropoietin, ESRD: End-stage Renal Disease, AE: Adverse events, EPO: Erythropoietin, PRCA: Pure Red Cell Aplasia

Serial Number	Author/Year	Study Design	Population	Relevant Conclusive Points
1	Lee et al. / 2009	Randomized Controlled Trial	78 adult HD patients were randomly assigned to either receive IV or SC epoetin. The time to Vascular access failure was	Patients in the SC therapy group exhibited a significantly higher rate (12.0%/patient year) of access failure as compared to the IV epoetin group

			analysed. Seven patients were withdrawn from evaluation due to various reasons.	(4.7%/patient year). The study was limited, however, by a small sample size and asymmetry between the two groups.
2	Klinkmann et al. / 1992	Clinical Trial (Prospective, Multi-center study)	362 adult HD patients from 16 European dialysis centers entered the study with half of the patients receiving r-HuEPO during the first year (first phase) of the trial and then serving as the control group during the second year (second phase) and the other half followed the opposite treatment plan. These patients were monitored for the drug safety of SC administered EPO. A total of 73 patients dropped out from the study.	Adverse events (AE) were recorded in the two groups, as serious and non-serious. AE were higher in the SC therapy group (55.9%) compared to the control group (44.1%), with serious AE being slightly higher in the therapy group. Statistically however, there was no significant difference between the two groups in terms of serious AE like hypertension, loss of vascular site access, respiratory and gastrointestinal system-related issues. Death due to cardiac issues was higher in the control group. NO anti-EPO antibodies were detected in either group. SC EPO administration has

				demonstrated a better safety profile than IV EPO.
3	Schaller et al. / 1994	Clinical Trial (Randomized, double-blind, Prospective, Multi-center study)	90 adult HD patients already suffering from ESRD, were enrolled and randomly assigned to 4 different groups, 2 of which comprised of IV EPO therapy and the other 2 SC EPO therapy. The study involved 4 different phases of treatment.	30% of all treated patients exhibited hypertensive reactions. During the Hb and hematocrit correction phase, there were more patients becoming hypertensive with SC EPO therapy than with IV EPO. This was not the case during the maintenance phase of treatment, however, SC EPO-treated patients did not complain about injection site pain and adverse reactions. The relationship between EPO treatment, development of hypertension and route of EPO administration is complex and multifactorial.
4	Kharagjitsingh et al. / 2005	Multi-center Cohort study	Existing patient data and serum samples from 1677 patients participating in The Netherlands	EPO hyporesponsiveness has numerous causes, prominently infection, inflammation and depletion of iron stores.

			Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD-2) were used in this study. Data was collected at 6-month intervals between April 1997 and September 2002. The study was performed to detect EPO hyporesponsive patients, EPO antibodies and PRCA in dialysis patients.	57 patients were found to be EPO hyporesponsive, an estimated incidence of 16.7/1000 patient years on EPO while on dialysis. Only one patient among the above 57 patients was found to have clinical PRCA, an estimated incidence of 0.29/1000 patient years on EPO while on dialysis. The incidence of EPO antibodies stood at 1.27/1000 patient-years since the start of dialysis. Out of these 57 patients found to be EPO hyporesponsive, 6 were treated with EPO IV, while all others used EPO SC. anti-EPO antibodies and PRCA remain a rare cause of EPO hyporesponsiveness, though it may be tied to SC EPO administration.
5	Navarro et al. / 1995	Clinical Trial	13 chronic haemodialysis patients, who remained	At the end of the first month of the switch to SC rHuEPO, there was a significant drop in pre-

			hypertensive after being on long term (>12 months), thrice weekly, post HD IV rHuEPO therapy were selected for this study, with hypertension being defined as elevated blood pressure that necessitated the use of anti-hypertensive medications. These patients were switched to SC EPO thrice weekly for 6 months, whilst keeping the total weekly SC dose at two-third of the weekly IV rHuEPO dose. Their blood pressure was monitored prior to each HD session. Patient's hypertensive therapy and red blood cell indices were also analysed regularly.	dialysis mean arterial pressure as opposed to baseline pressures, prior to the switch. The number of hypertensive patients reduced from 13 at the time of baseline recording to 8 at the end of the six-month trial. In the remaining 8 hypertensive patients, the severity dropped significantly as was measured by a "therapeutical score" that assessed hypertensive severity from the antihypertensive power of the drugs used to control it. This study shows better control of hypertension with the SC route of administration in ESRD patients and that SC rHuEPO doesn't prevent hypertension in ESRD patients, rather only reduces its severity compared to the IV route.

Drug-associated Costs[2]

Patients with severe anemia secondary to CKD < Hb 9.0 gm/dl and those with advanced CKD, for example those on regular HD, need prolonged periods of ESA therapy to improve their QoL, to prevent anemia-related symptoms, and to minimize the need for blood transfusion. This can incur significant recurring costs on individuals and on healthcare systems. Dealing with this by employing a cost effective yet efficacious means of ESA therapy is therefore crucial (see Table 5).

Table 5. **A summary of studies comparing healthcare costs between intravenous and subcutaneous EPO administration**

HD: Haemodialysis, SC: Subcutaneous, IV: Intravenous, EPO: Erythropoietin, CKD: Chronic Kidney Disease, CAD: Canadian Dollars

Serial Number	Author/date	Study design	Population	Main points
1	Wazny et al. / 2013	Retrospective Multicenter Study	Patients were chosen from 4 in-centre Haemodialysis Units in Winnipeg, Manitoba, Canada. Patients were treated with Epoetin-alfa in two separate treatment regimes in two separate time periods - each lasting 6 months. 622 individuals were subject to on IV EPO (period 1), and 609 individuals to SC EPO (period 2). Costs were analysed retrospectively from available patient	The switch from IV to SC EPO across 4 haemodialysis units, resulted in a 12.6% dose reduction and saved 98% of the patients receiving SC epoetin alpha, about 1125 USD per person per year.

			data and monthly inventory billing records.	
2	Galliford et al. / 2005	Comparative Study (prospective cohort)	86 adult HD patients, already on SC EPO-alfa treatment, were switched simultaneously to IV EPO-alfa, at the same weekly dose as their SC administration, for a period of 6 months. Monthly Red cell indices, weekly EPO dosages and other parameters were monitored during the study.	Transitioning from SC to IV EPO alpha in HD patients requires a dose increase of around one-third, possibly resulting in an annual increase in cost of £ 1500 per patient.
3	McFarlane et al. / 2007	Controlled Clinical Trial	158 adult, chronic, HD patients, already on IV EPO therapy, were studied for 1 year prior to the trial. In the study that spanned 12 months, patients were collectively shifted to SC EPO therapy.	The cost of anemia therapy rose significantly 6 months post-switch to IV EPO therapy. The median rise in costs over the whole 6-month period was estimated at 13.1% (CAD 665/patient-year; $p < 0.01$).
4	Prasad et al. / 2020	Retrospective Observational Study	Two hundred and fifteen patients aged more than 18 years, receiving in-center HD for at least 6 months at 4 HD centers.	Administering epoetin alpha subcutaneously resulted in a dose reduction from IV to

			Patients suffering from anemia of CKD requiring epoetin alfa therapy, and on IV epoetin alfa therapy for at least 6 months, were switched to SC EPO-alfa. Data was collected from 6 months prior to 12 months after the switch. Primary outcome was the assessment of epoetin-alfa cost per patient per month before and after the policy change.	SC of 30.51% and 25% reduction in EPO costs, being equally effecting at maintaining Hb levels in patients on HD.

Drug Efficacy[2]

There are various factors that underpin ESA efficacy, i.e., the dose needed to attain a certain target Hb concentration or hematocrit level, which can be adequately summarized under the umbrella of individual ESA pharmacokinetics and pharmacodynamics. Discussed further are factors that have been found relevant to ESA efficacy. Numerous studies have provided support to the SC route of administration due to multiple advantages over the IV route, most notably a lower overall dose to achieve a similar target Hb concentration as well as hematocrit levels and a reduced dosing frequency, i.e., the SC route offers more efficacy for administration of r-HuEPO. Although the SC route offers a much lower level of bioavailability as compared to the IV route, it results in a significantly longer half-life, attaining peak plasma levels that are substantially lower than the IV route but persist for a much longer period of time. The reasons theorized behind this low bioavailability but a paradoxically prolonged maintenance of modest serum plasma levels can be attributed to a multiple injection site, drug inherent and systemic factors. This persistence and delayed absorption of EPO from SC administration has been pivotal in the explanation for this route's effectiveness over the IV route. As erythropoiesis is not as dependent on peak plasma EPO levels as it is on the maintenance of EPO levels above a critical threshold for a prolonged time duration, the SC route offers an advantage. IV EPO

dosing results in a fall in serum r-HuEPO levels during the interdialytic period and ultimately in the apoptosis of EPO-dependent erythrocyte precursor cells in the bone marrow. SC EPO dosing prevents this apoptosis due to maintenance of plasma EPO levels for a longer duration therefore enabling a more protracted, efficient and effective process of erythropoiesis.

Table 6. **A brief summary of studies comparing erythropoietin pharmacokinetics between intravenous and subcutaneous administration**

HD: Haemodialysis, PD: Peritoneal Dialysis, CAPD: Continuous Ambulatory Peritoneal Dialysis, SC: Subcutaneous, IV: Intravenous, IP: Intra-peritoneal, Hb: Haemoglobin, EPO: Erythropoietin, rHuEPO: Recombinant Human Erythropoietin, ESRD: End-stage Renal Disease, rcEPO: Recombinant Human Erythropoietin, C_{max}: Peak serum drug concentration, $t_{1/2}$: drug half-life, S.D.: Standard Deviation

Serial Number	Author / Year	Study Type	Population	Relevant Conclusive points
1	Brockmöller et al. / 1992	Prospective study	12 adult, chronic, stable HD patients, already under treatment with a thrice weekly IV rcEPO, were subjected to treatment scheme using regimes of IV and SC rcEPO recombinant human EPO (rcEPO) injections in discrete phases to assess pharmacokinetics and therapeutic response to both routes. Serum analyses were carried out at specific time intervals for achieving the goals of this study.	After first dosing with IV EPO, plasma EPO levels were found to have a mean (±S.D.) half-life of 5.4 ± 1.70 hours compared to initial SC EPO administration with a mean(± S.D) absorption time being 22 ± 11 and an average bioavailability of 44% (28-100%). With continuous long-term treatment with IV EPO, elimination half-life reduced by 15% to

				around 5 hours, possibly a reflection of an increase in hematocrit. The study suggests that the SC route be more effective due to prolonged plasma rcEPO elevation following SC administration, with the exact mechanism being unclear.
2	Nielsen / 1990	Clinical Trial	Two groups of adult, chronic, and stable HD patients were enrolled. Group 1 was already under maintenance treatment with IV recombinant human EPO (rhEPO) thrice weekly. Group 2 included ESRD patients not previously treated with rhEPO. Both groups were subjected to IV and SC rhEPO administration at different dosages – 50 U/kg for group 1 and 150 U/kg for group 2. Pharmacokinetic studies were then carried out using serum analytics.	After IV rhEPO injections at the lower dose, the mean half-life was found to be 5.4 ± 0.90 hrs, while at the higher dose it was around 7.60 hrs. Peak serum EPO levels (C_{max}) after IV dosing were found to be 20 times that of SC C_{max}. Peak serum EPO levels after SC dosing were reached on an average of 27.3 ± 8.6 hrs. Mean bioavailability was also found to be a meager 14.1% after

				SC dosing. Despite the data, the protracted maintenance of rhEPO levels after SC administration may be more efficacious than IV dosing though more work is needed in this area and patients with SC administration need to be closely monitored for anti-EPO antibodies.
3	Neumayer et al. / 1989	Clinical Trial	29 adult, chronic, and stable HD patients, were enrolled and split into 3 groups. Group I comprised of 19 patients who were treated with IV rhEPO initially, then kept on maintenance therapy for 3 months and thereafter 10 patients from this group, making up group II, were subject to another bolus dose of IV rhEPO at the end of these 3 months. Group III was made up of 9 additional patients who were treated with a single SC rhEPO dose. Pharmacokinetic profiles of these two administration	Peak plasma levels after IV dosing were seen within 5 minutes of administration and were not significantly different between Group I and II. IV rhEPO elimination half-life was found to be an average of 8.75 (7.29 - 11.68) hours, in Group I, but fell significantly after 3 months, i.e. in Group II, to 6.80 hours. SC rhEPO peak levels, though 5% that of IV levels, were attained between 18-24 hours

			routes at different stages of treatment was then assessed using serum studies.	after administration, with a mean half-life of 11.2 (7.0-13.9) hrs. SC bioavailability was also low at around 25%. The study questions the benefit of reaching high peak serum levels immediately after IV administration and provides support to a relatively low dose SC administration as mimicking EPO physiological levels in augmenting erythropoiesis.
4	Ateshkadi et al. / 1993	Clinical Trial	8 stable peritoneal dialysis (PD) patients participated in a randomized, single-dose, three-way cross-over study with Continuous Ambulatory PD (CAPH) being carried throughout the study. Patients were already using EPO or candidates for it. They were given a single average dose of 99.1 U/kg of intraperitoneal (IP), IV, and SC rhEPO. Pharmacokinetics of the	C_{max} for the IP and SC routes are almost identical but only 5% of the IV route. Peak plasma concentrations (C_{max}) were attained at a mean of 9.4 ± 1.90 hrs for the IP route, compared to a much slower time for SC, at 17.1 ± 5.0 hours. However, SC bioavailability, 22.81%, was twice that

			three routes were compared using serum analysis studies.	of IP EPO, 11.4%. Compared to the IP route, the SC route had a significantly higher area-under-the-curve (AUC) between 0 and 96 hours after administration. The study also found the potential effect of EPO administration into a "dry" or empty peritoneum for greater efficacy via this route, albeit significantly lesser than the SC route. Administration strategies involving a more prolonged EPO absorption with a relatively low C_{max} may enable more efficacy of rhEPO.
5	Macdougall et al. / 1989	Clinical Trial	8 adult, stable, chronic CAPD patients were enrolled. Each patient was administered intraperitoneal (IP), IV, and SC rhEPO at a set dose for each route. The doses were spaced by 4 weeks.	IV administration exhibited a serum peak level being attained at 15 minutes post administration, with a mean half-life ($t_{1/2}$) of 8.20 (6.20 - 10.20) hrs. IP administration saw C_{max} at 12 hours and an

				average bioavailability of 2.90% (1.2 - 6.8%). C_{max} for SC administration was at 18 hours and had a mean bioavailability of 21.5% (11.3 - 36.0%). The study found that $t_{1/2}$ for IV EPO in CAPD patients was not significantly different from those on HD. The findings of the study also suggest that high serum peaks of EPO are of little therapeutic value for effective erythropoiesis. As a result, it suggests that SC route of administration may be more beneficial in both CAPD and HD patients. The bioavailability of this route, however, is governed by a complex interplay of injection site, drug composition and systemic factors.

Route of Administration and Stage of CKD (Non-Dialysis Dependent and Patients on Peritoneal Dialysis vs Haemodialysis Patients) [2]

Non-dialysis CKD patients with preserved GFR, or those undergoing peritoneal dialysis, benefit from SC administration of ESAs, considering that it's least invasive and can be carried out without any monitoring. Furthermore, intraperitoneal administration in patients on continuous ambulatory peritoneal dialysis (CAPD), can dilute ESA concentration, limiting its use. The advantage of IV administration lies in the fact that it can be conveniently administered during the process of haemodialysis. Numerous studies have shown that SC doses of ESAs in non-dialysis dependent and patients on peritoneal dialysis, were found to effectively increase Hb concentrations and were well-tolerated and may even be more efficacious than IV EPO formulations in HD patients as well. However, more work needs to be done comparing the efficacy of SC versus IV EPO administration in non-dialysis and patients on continuous ambulatory peritoneal dialysis (see Table). The use of EPO in HD patients has been covered under other sections.

Table 7. **A comparison of the different routes of ESA administration with the stage of CKD (Non-dialysis dependent AND Patients on Peritoneal Dialysis vs Haemodialysis patients)**

HD: Haemodialysis, PD: Peritoneal Dialysis, CAPD: Continuous Ambulatory Peritoneal Dialysis, SC: Subcutaneous, IV: Intravenous, Hb: Haemoglobin, EPO: Erythropoietin, r-HuEPO: Recombinant Human Erythropoietin, ESRD: End-stage Renal Disease, CKD: Chronic Kidney Disease, QoL: Quality of Life

Serial Number	Author/date	Study Design	Population	Main Points
1	Hughes et al. / 1990	Randomized Controlled Trial	15 adult ESRD patients, on CAPD for the treatment of ESRD were enrolled in this study. They were subjected to treatment	Thrice weekly administration of r-HuEPO to subjects on peritoneal dialysis effectively corrected renal anemia. A

			with r-HuEPO thrice weekly SC, with two separate target Hb levels in two discrete phases – the correction phase and the maintenance phase.	reduction in ineffective erythropoiesis and much more importantly, an increase in erythroid activity was thought to be the major factor in increasing red cell volumes. The findings of this study also suggested that prolonged, moderate increase in serum EPO concentration is more important than a sudden rise in EPO as would be observed with IV EPO administration.
2	Montini et al. / 1993	Multi-center Study	24 children, suffering from anemia secondary to ESRD and on peritoneal dialysis, aged 3 months to 18 years, were treated with SC r-HuEPO, in varying doses, depending on the Hb levels achieved with each dose.	Eighteen patients experienced increased Hb levels after 24 weeks of treatment from a mean of 6.5 (4.7-7.9) gm/dl to 9.4 ± 1.7 gm/dl. The IV route of administration is less convenient in patients on peritoneal dialysis because of lack of vascular access and difficult self-treatment, while the intraperitoneal route of administration compromises

				bioavailability significantly.
3	Trivedi and Brooks / 2003	Comparative Study (retrospective)	31 pre-dialysis CKD patients' medical record was assessed. These patients had been treated with EPO between 1996 and 2001. Various parameters were assessed including renal function, red cell indices, and iron profiles.	The mean hematocrit increased from a baseline value of 28.4 ± 2.7 to 33.6 ± 3.4% after an average of 6 weeks of treatment and to 37.7 ± 4.5% after about 3 months of treatment. By analyzing a variety of other parameters as well, the study importantly concluded that pre-dialysis CKD patients exhibited significant response to EPO therapy without parenteral iron therapy. It was also evident that pre-dialysis CKD patients had lower overall EPO dosage requirements than ESRD patients. However, it is important to note that these findings are similar to the ones in ESRD patients. More work is specifically needed in pre-dialysis patients for analyzing dose

				requirements among the two routes.
4	Stevens et al. / 1991	Clinical Trial	Sixteen anemic patients with an Hb < 9 gm/dl, maintained on chronic continuous ambulatory peritoneal dialysis (CAPD), were given SC epoetin-alfa thrice weekly, in two different phases – each with a higher Hb level target than the previous one. The dose of SC EPO was changed periodically, depending upon the results of red-cell indices and target Hb levels.	15 patients responded to treatment with a rise in Hb concentration of more than 2 gm/dl. SC administration was found to be acceptable, convenient more effective in treating anemia in CAPD patients. It was also associated with an improved QoL and can very well be thought of as an optimal route of EPO administration in CAPD patients. Additionally, in the same dialysis unit, it was found that CAPD patients required a lower dose via the SC route than HD patients did via the IV route for maintaining target Hb levels.

Convenience of Drug Administration[2]

Between the two routes, convenience depends on factors like the stage of CKD, the dose and dosage frequency, the type of ESA being used, ease-of-use, the type of dialysis being utilized, the associated healthcare costs, and patient satisfaction.

For non-HD patients, the SC route may be more generally convenient due to the lack of a continuous IV access, the ease of self administration, comparatively lower dosage, less frequent hospital visits, a reduced dosing frequency and ultimately reduced costs. Even in HD patients, the SC route has been tied to similar advantages and may therefore be more beneficial overall as compared to the IV route, despite the obvious convenience that an arteriovenous fistula confers to IV EPO administration. This may be particularly beneficial in low-income countries where affordability and access to newer, longer acting ESAs may be difficult. Evidence lending support to the efficacy, cost effectiveness and safety of the SC route of ESA administration has been presented in earlier sections.

A multicenter study, non-randomized, open-label study conducted by Grzeszczak et al. in 128 stable, chronic PD patients already on once to thrice-weekly SC EPO administration who were enrolled in a study where the effect of shifting them to once-weekly and once-fortnightly administration of SC Epoetin-beta in maintaining their Hb concentrations, was investigated. The findings concluded that shifting patients to SC Epoetin-beta once-weekly did not result in a significant change in mean Hb levels over a period of 25 weeks. In the once-fortnightly group, the dose needed to be increased slightly and even then, more than 50% of patients could still be maintained on baseline EPO-beta doses or lower. This study paves way for a means of ESA administration that could result in greater convenience, compliance, patient satisfaction, reduced dosage frequency and greater cost savings.

The convenience of use for the IV formulation in HD has its possible roots in the preference for its use by HD Staff. This may be due to the routine use of the IV route by HD staff as well as the issue of pain or ‘stinging’ or discomfort at the injection site associated with the initial use of SC epoetin-alfa which some studies have cited in the past. The KDIGO guidelines have also cited ‘pain’ secondary to SC administration, in terms of using short-acting ESAs, as a reason to prefer IV EPO administration, referring to the results of a single centre trial of 30 patients. In a randomized, un-blinded trial carried out by Kaufman et al. among 208 patients, 86% of the 107 candidates who received SC epoetin injections reported experiencing pain as none to mild. Similar findings were found in a multi-center randomized, double-blind,

prospective study among 90 ESRD patients already on HD, who were subjected to different regimes of IV and SC EPO treatment. None of the patients treated SC complained of injection site pain nor were there any identifiable local adverse reactions. Nonetheless the pain reported in previous studies has mainly been tied to the citrate component of the epoetin-alfa buffered solution that is administered SC to patients. However, it has largely been controlled by replacement of the citrate preservative with Benzyl Alcohol saline and other newly developed stabilizer solutions, using large gauge needles, and smaller volume doses, all of which were highly effective in reducing pain whilst maintaining drug efficacy.

References:

1. Ng T, Marx G, Littlewood T, Macdougall I. Recombinant erythropoietin in clinical practice. *Postgrad Med J*. 2003;79(933):367-376.
2. Shahab MH, Saifullah Khan S. Erythropoietin Administration for Anemia Due to Chronic Kidney Disease - Subcutaneous OR Intravenous, What Do We Know So Far?. *Cureus*. 2020;12(9):e10358.

Survey Form

1. What percentage of your patients are diagnosed with anemia in your clinical practice?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%

2. Have you ever prescribed Human Recombinant Erythropoietin (rEPO) for anemia?

a) Yes, regularly

b) Yes, occasionally

c) No, rarely

3. What conditions or diseases do you commonly treat with rEPO in your practice?

a) Chronic kidney disease

b) Cancer-related anemia

c) Anemia of chronic disease

d) Anemia due to chemotherapy

4. What is your primary goal when prescribing rEPO for anemia?

a) To increase hemoglobin levels

b) To reduce the need for blood transfusions

c) To improve overall patient quality of life

d) To address symptoms of fatigue

5. What is your approach to adjusting rEPO dosage in patients with fluctuating hemoglobin levels?

a) Increase the dose immediately

b) Decrease the dose immediately

c) Wait and monitor for a consistent trend before adjusting

d) Consult with a hematology specialist

6. How long do you typically wait to assess the initial response to rEPO therapy in your patients?

a) 1 week

b) 2 weeks

c) 4 weeks

d) 6 weeks

7. How effective do you find rEPO in raising hemoglobin levels and managing anemia?

a) Very effective

b) Effective

c) Moderately effective

d) Not very effective

8. How do you monitor the progress of patients receiving rEPO treatment for anemia?

a) Regular hemoglobin tests

b) Symptom improvement checks

c) Quality of life assessments

d) Bone marrow analysis

9. What factors influence your decision on the appropriate rEPO dosage for a patient?

a) Hemoglobin levels

b) Patient age and overall health

c) Type and severity of anemia

d) Presence of other medical conditions

10. How often do you adjust the rEPO dosage during treatment based on patient response?

a) Frequently

b) Occasionally

c) Rarely

11. In your experience, what are the most common side effects of rEPO treatment?

a) High blood pressure

b) Blood clots

c) Pure red cell aplasia

d) No significant side effects

12. Do you consider patient lifestyle factors (e.g., diet, exercise) when prescribing rEPO?

a) Yes, always

b) Yes, sometimes

c) No, rarely

d) No, never

13. What is your typical follow-up schedule for patients on rEPO therapy?

a) Weekly

b) Bi-weekly

c) Monthly

d) Every two months

14. Have you seen cases where patients did not respond well to rEPO therapy?

a) Yes, frequently

b) Occasionally

c) Rarely

15. How do you typically manage anemia in patients who do not respond to rEPO therapy?

a) Increase the dose of rEPO

b) Add or increase iron supplementation

c) Switch to alternative anemia treatments

d) Consider blood transfusions

Survey Findings

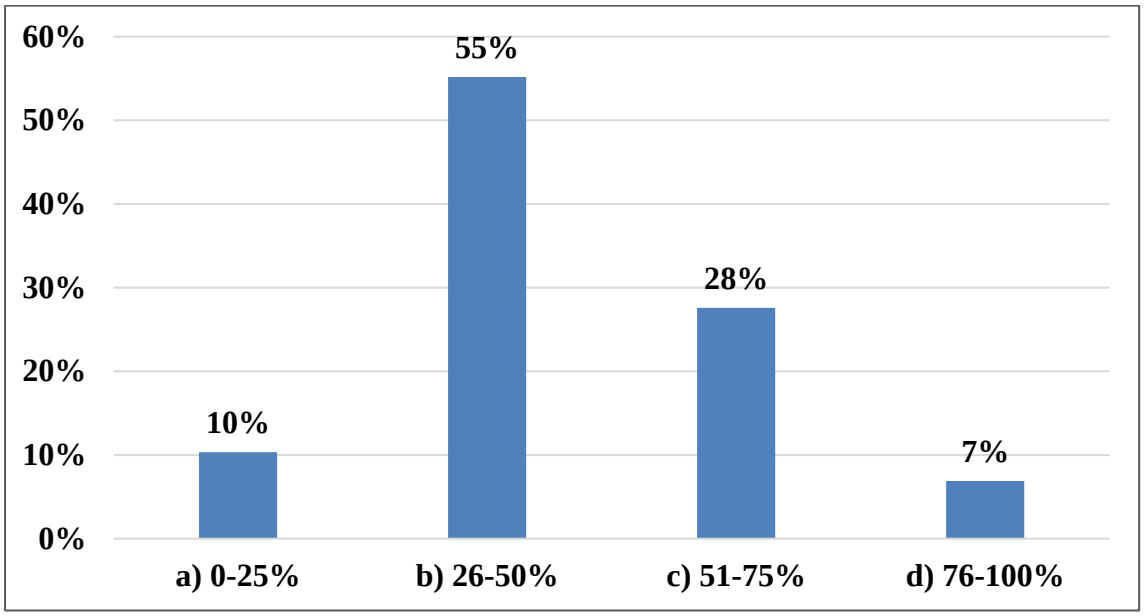
1. What percentage of your patients are diagnosed with anemia in your clinical practice?

a) 0-25%

b) 26-50%

c) 51-75%

d) 76-100%



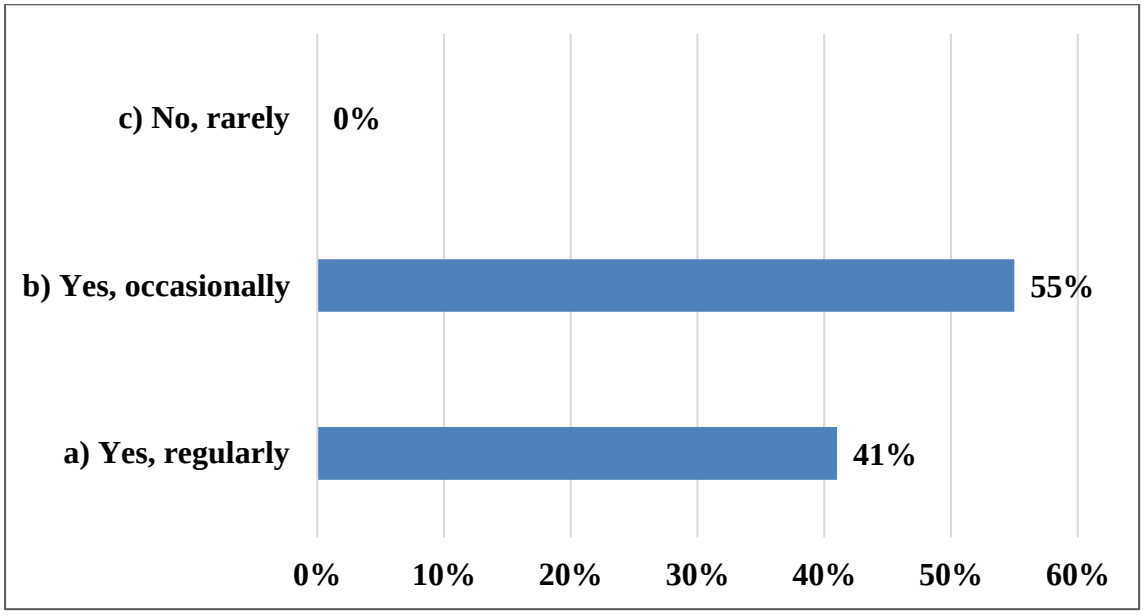
According to 55% of doctors, 26-50% of their patients are diagnosed with anemia in their clinical practice.

2. Have you ever prescribed Human Recombinant Erythropoietin (rEPO) for anemia?

a) Yes, regularly

b) Yes, occasionally

c) No, rarely



55% of doctors have occasionally prescribed Human Recombinant Erythropoietin (rEPO) for anemia.

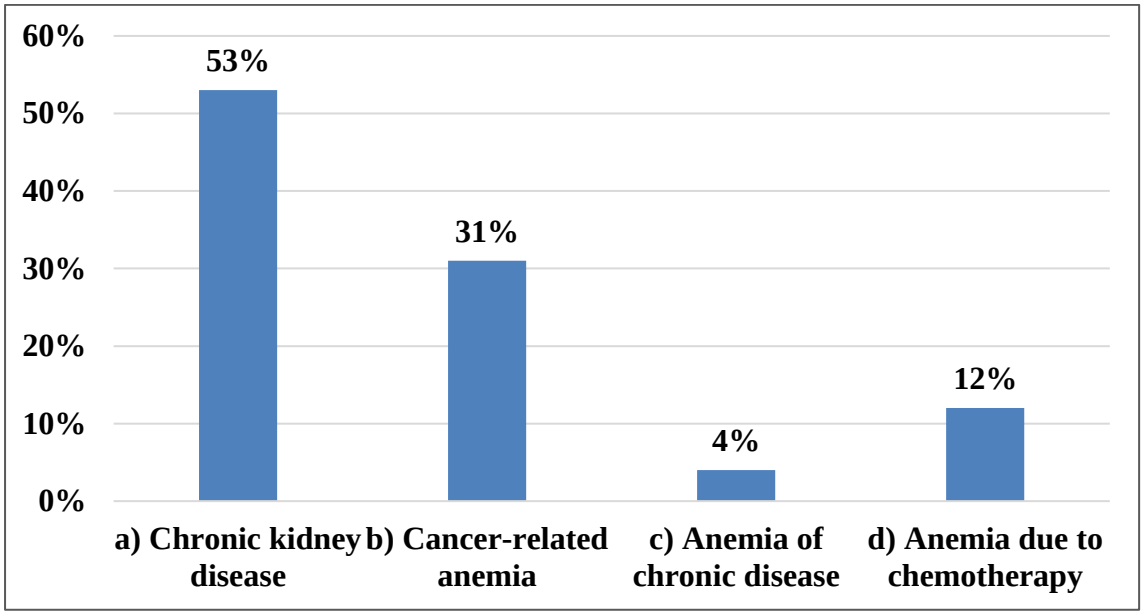
3. What conditions or diseases do you commonly treat with rEPO in your practice?

a) Chronic kidney disease

b) Cancer-related anemia

c) Anemia of chronic disease

d) Anemia due to chemotherapy



53% of doctors commonly treat chronic kidney disease with rEPO in their practice.

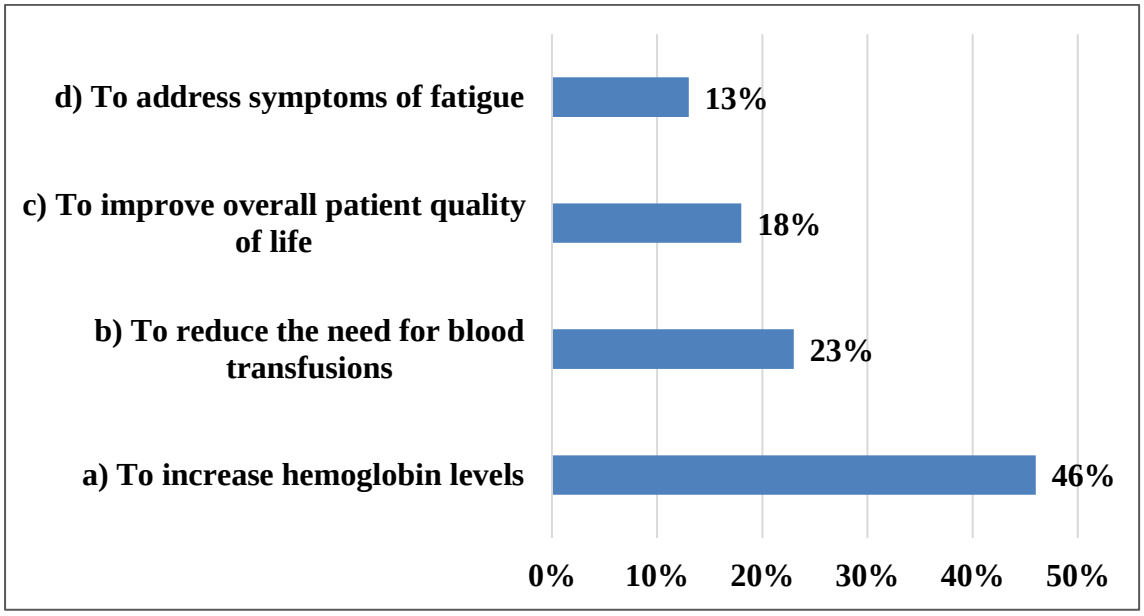
4. What is your primary goal when prescribing rEPO for anemia?

a) To increase hemoglobin levels

b) To reduce the need for blood transfusions

c) To improve overall patient quality of life

d) To address symptoms of fatigue



When prescribing rEPO for anemia, the primary goal of 46% of doctors is to increase hemoglobin levels.

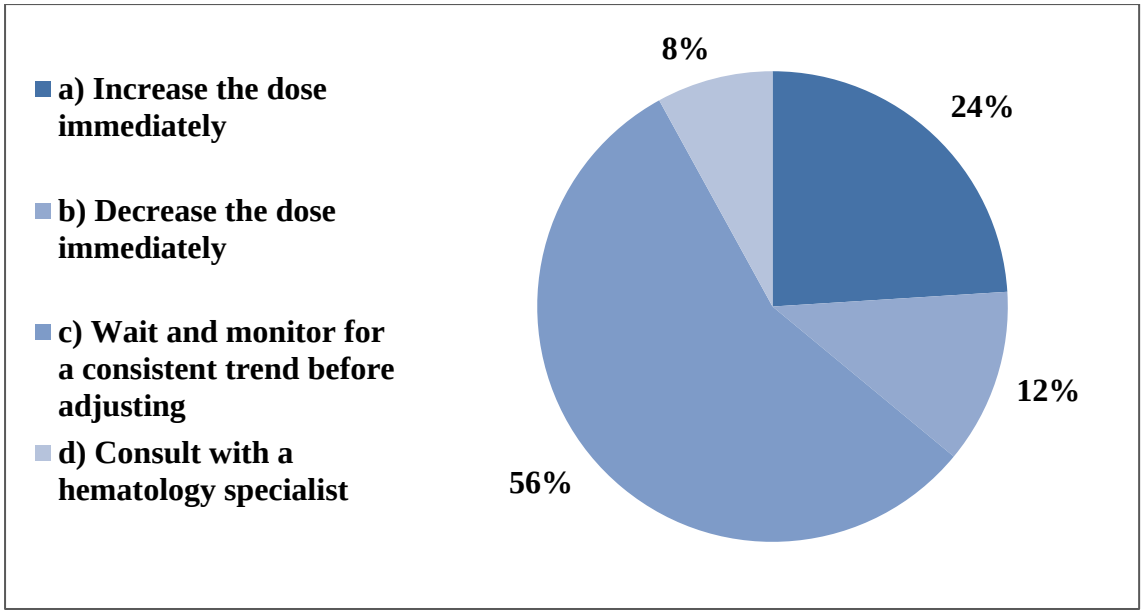
5. What is your approach to adjusting rEPO dosage in patients with fluctuating hemoglobin levels?

a) Increase the dose immediately

b) Decrease the dose immediately

c) Wait and monitor for a consistent trend before adjusting

d) Consult with a hematology specialist



56% of doctors adopt the approach of wait and monitor for a consistent trend before adjusting rEPO dosage in patients with fluctuating hemoglobin levels.

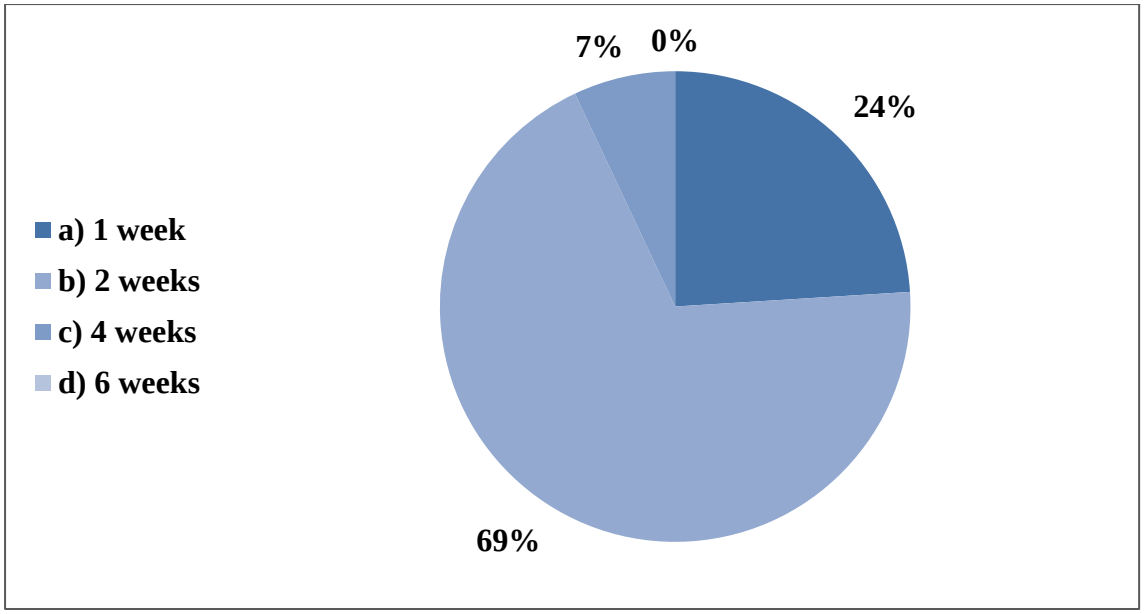
6. How long do you typically wait to assess the initial response to rEPO therapy in your patients?

a) 1 week

b) 2 weeks

c) 4 weeks

d) 6 weeks



According to majority of doctors, 69%, they typically wait 2 weeks to assess the initial response to rEPO therapy in their patients.

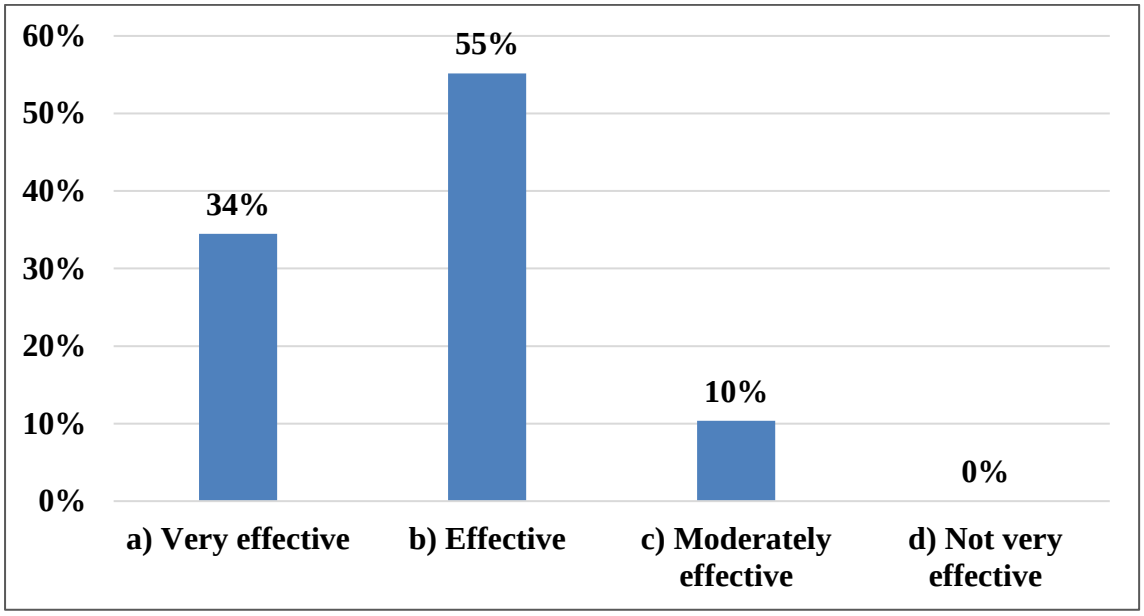
7. How effective do you find rEPO in raising hemoglobin levels and managing anemia?

a) Very effective

b) Effective

c) Moderately effective

d) Not very effective



55% of doctors find rEPO effective in raising hemoglobin levels and managing anemia.

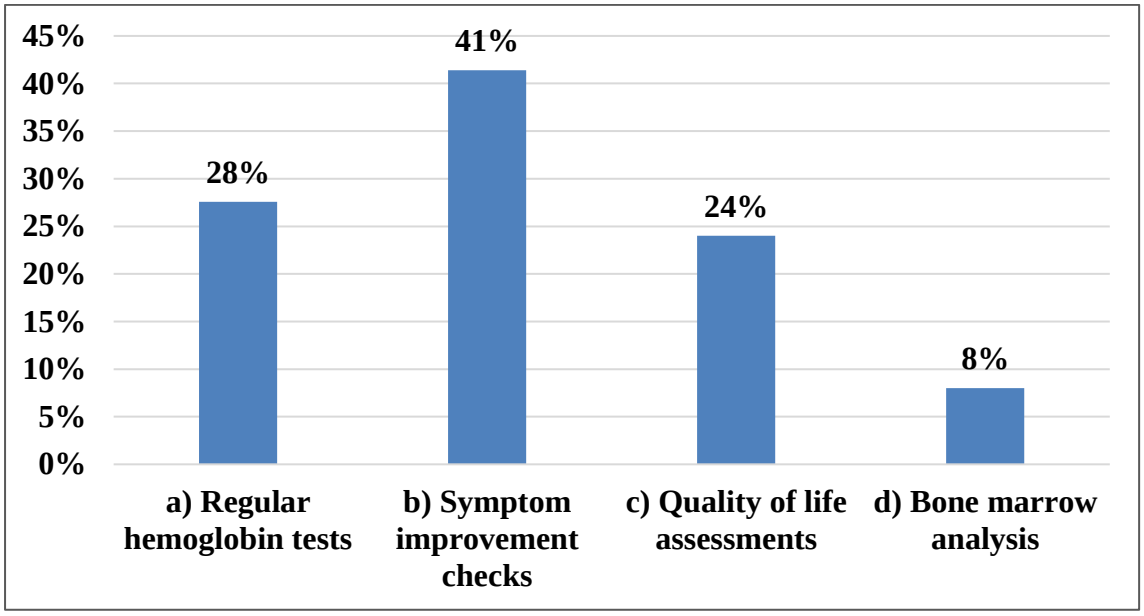
8. How do you monitor the progress of patients receiving rEPO treatment for anemia?

a) Regular hemoglobin tests

b) Symptom improvement checks

c) Quality of life assessments

d) Bone marrow analysis



As per 41% of doctors, they monitor the progress of patients receiving rEPO treatment for anemia by symptom improvement checks.

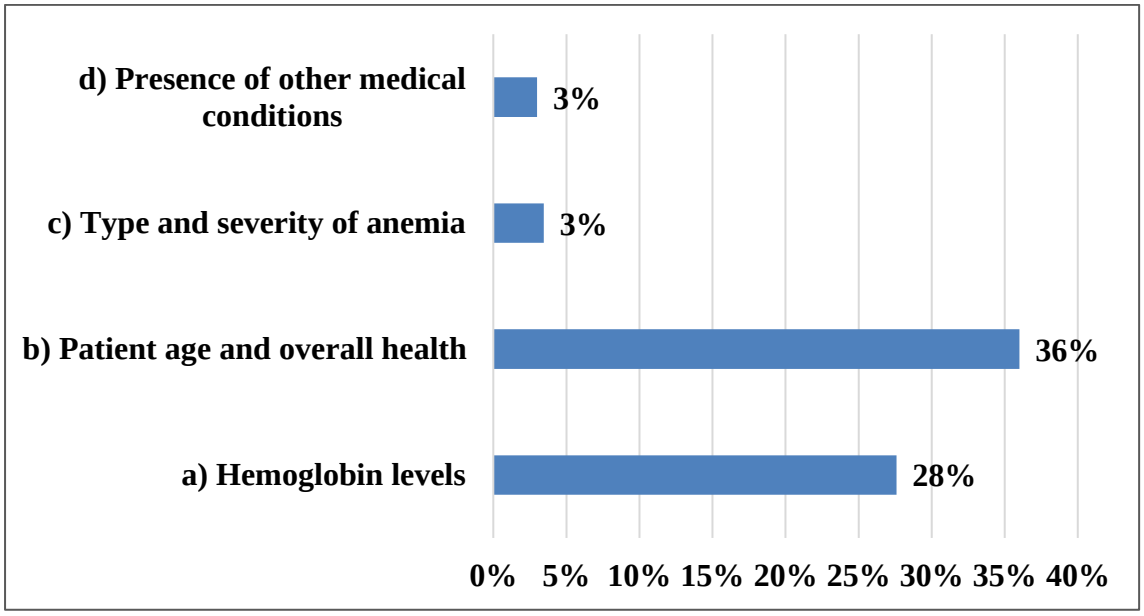
9. What factors influence your decision on the appropriate rEPO dosage for a patient?

a) Hemoglobin levels

b) Patient age and overall health

c) Type and severity of anemia

d) Presence of other medical conditions



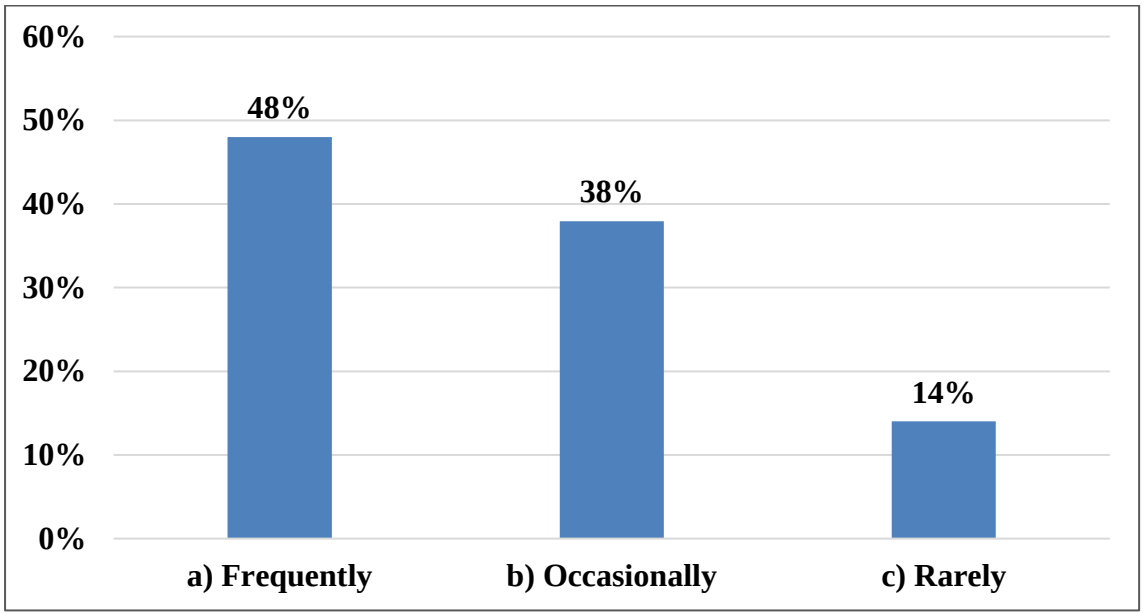
According to 36% of doctors, patient age and overall health influence their decision on the appropriate rEPO dosage for a patient.

10. How often do you adjust the rEPO dosage during treatment based on patient response?

a) Frequently

b) Occasionally

c) Rarely



According to 48% of doctors, they frequently adjust the rEPO dosage during treatment based on patient response.

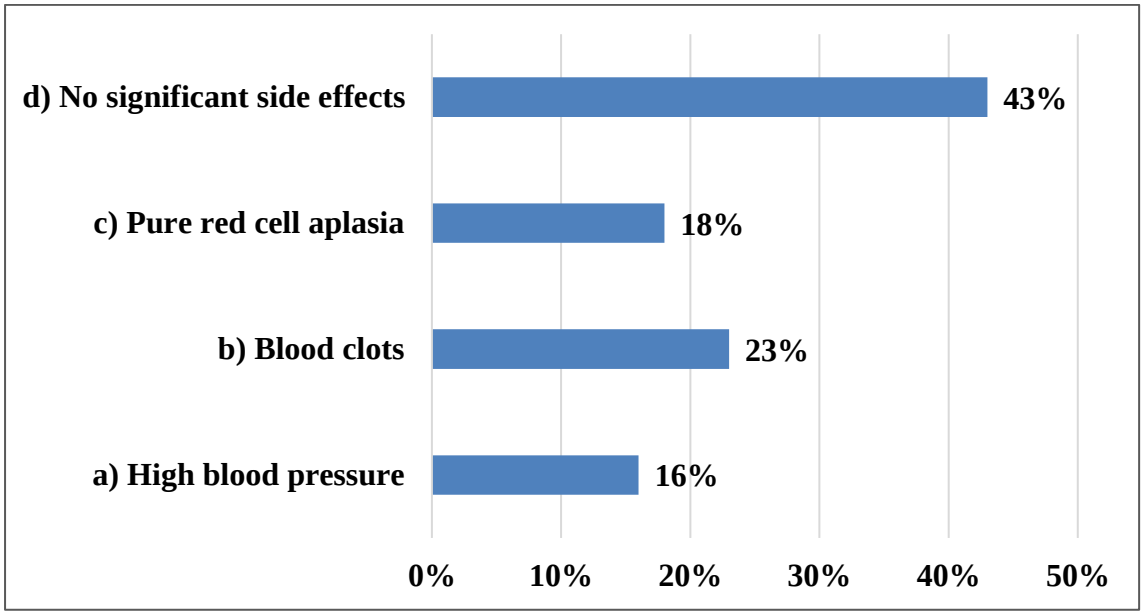
11. In your experience, what are the most common side effects of rEPO treatment?

a) High blood pressure

b) Blood clots

c) Pure red cell aplasia

d) No significant side effects



In the experience of 43% of doctors, there are no common side effects of rEPO treatment.

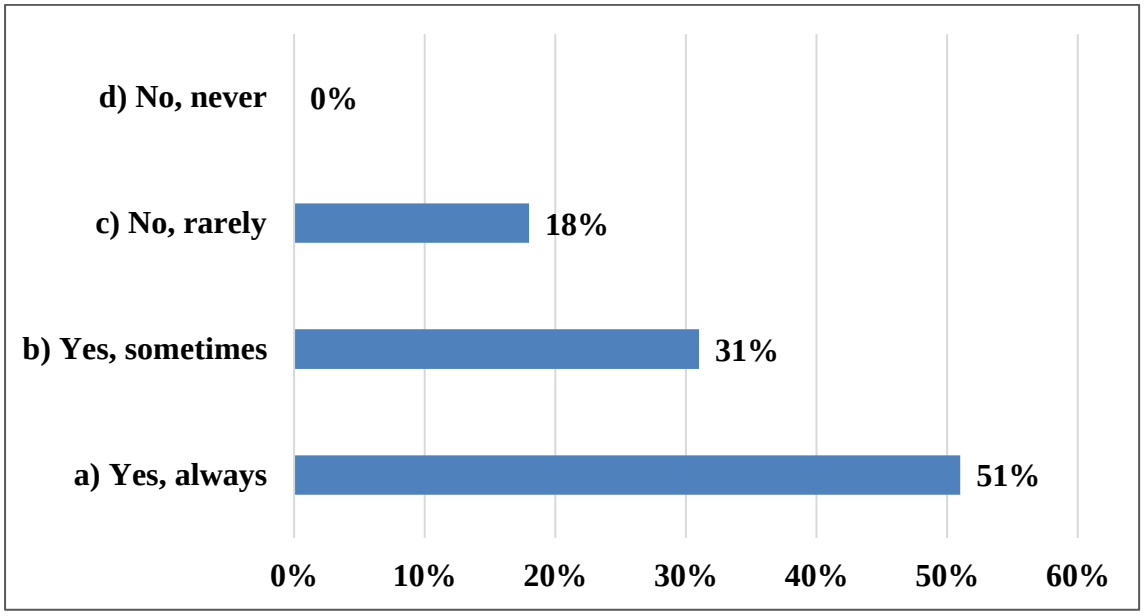
12. Do you consider patient lifestyle factors (e.g., diet, exercise) when prescribing rEPO?

a) Yes, always

b) Yes, sometimes

c) No, rarely

d) No, never



51% of doctors always consider patient lifestyle factors.

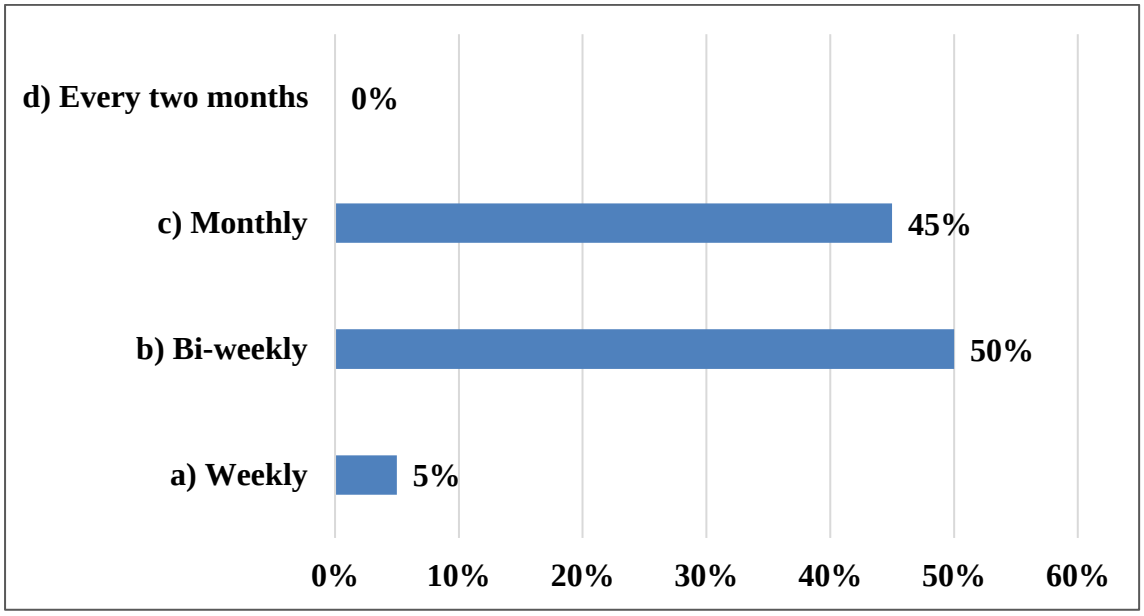
13. What is your typical follow-up schedule for patients on rEPO therapy?

a) Weekly

b) Bi-weekly

c) Monthly

d) Every two months



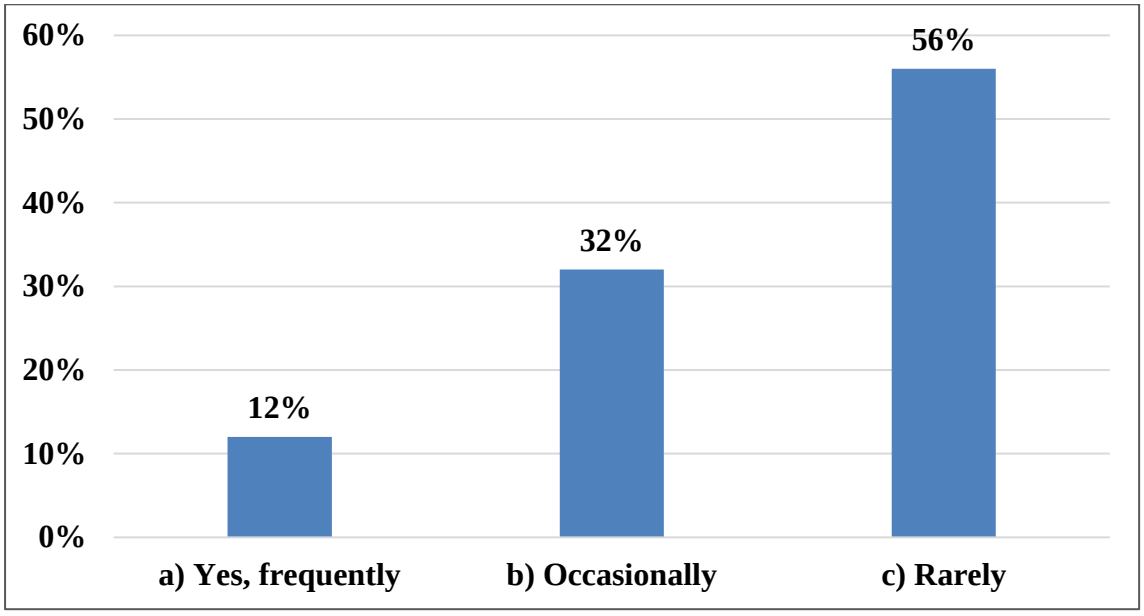
As per 50% of doctors, their typical follow-up schedule for patients on rEPO therapy is bi-weekly.

14. Have you seen cases where patients did not respond well to rEPO therapy?

a) Yes, frequently

b) Occasionally

c) Rarely



56% of doctors shared that they have rarely seen cases where patients did not respond well to rEPO therapy.

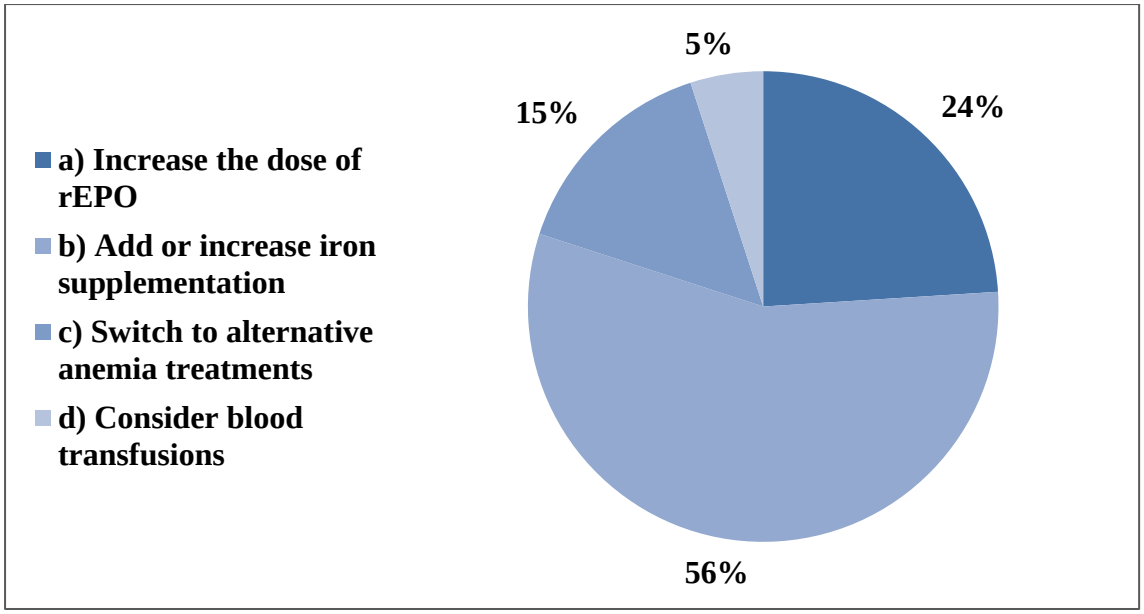
15. How do you typically manage anemia in patients who do not respond to rEPO therapy?

a) Increase the dose of rEPO

b) Add or increase iron supplementation

c) Switch to alternative anemia treatments

d) Consider blood transfusions



According to 56% of doctors, they typically manage anemia in patients who do not respond to rEPO therapy by adding or increasing iron supplementation.

Summary

- According to 55% of doctors, 26-50% of their patients are diagnosed with anemia in their clinical practice.
- 55% of doctors have occasionally prescribed Human Recombinant Erythropoietin (rEPO) for anemia.
- 53% of doctors commonly treat chronic kidney disease with rEPO in their practice.
- When prescribing rEPO for anemia, the primary goal of 46% of doctors is to increase hemoglobin levels.
- 56% of doctors adopt the approach of wait and monitor for a consistent trend before adjusting rEPO dosage in patients with fluctuating hemoglobin levels.
- According to majority of doctors, 69%, they typically wait 2 weeks to assess the initial response to rEPO therapy in their patients.
- 55% of doctors find rEPO effective in raising hemoglobin levels and managing anemia.
- As per 41% of doctors, they monitor the progress of patients receiving rEPO treatment for anemia by symptom improvement checks.
- According to 36% of doctors, patient age and overall health influence their decision on the appropriate rEPO dosage for a patient.
- According to 48% of doctors, they frequently adjust the rEPO dosage during treatment based on patient response.
- In the experience of 43% of doctors, there are no common side effects of rEPO treatment.
- 51% of doctors always consider patient lifestyle factors.
- As per 50% of doctors, their typical follow-up schedule for patients on rEPO therapy is bi-weekly.
- 56% of doctors shared that they have rarely seen cases where patients did not respond well to rEPO therapy.
- According to 56% of doctors, they typically manage anemia in patients who do not respond to rEPO therapy by adding or increasing iron supplementation.

Consultant Opinion

Market Opportunities:

- There is an opportunity to increase the use of rEPO by educating doctors about its benefits and effective use, especially in CKD-related anemia. Pharmaceutical companies can provide continuing medical education (CME) sessions focusing on the latest research and guidelines for rEPO therapy.
- Develop and offer decision-support tools that help doctors assess when and how to adjust rEPO dosages based on patient-specific factors, thus improving the precision of anemia management.

Value for Healthcare Professionals:

- Provide comprehensive clinical data and treatment guidelines to assist doctors in making informed decisions about rEPO use. This can help in achieving better patient outcomes and adherence to best practices.
- Equip healthcare professionals with resources to educate patients about rEPO therapy, its benefits, potential side effects, and the importance of adherence.

Adverse Effect Management:

- Establish and disseminate protocols for monitoring side effects, even if they are not commonly observed. This proactive approach can help in early detection and management of any adverse reactions.
- Provide training sessions focused on managing potential side effects and non-response to rEPO therapy. This can help healthcare professionals feel more confident in prescribing and managing rEPO treatments.

Withdrawal Management:

- Develop clear guidelines for transitioning patients off rEPO therapy when necessary. This can include gradual dose reduction strategies and alternative treatment options to ensure continuity of care.

Market Positioning:

- Emphasize the benefits of rEPO, such as its effectiveness in increasing hemoglobin levels and managing anemia, particularly in CKD patients. Use testimonials and case studies to showcase success stories.
- Conduct and share comparative studies that highlight the superior effectiveness and safety profile of rEPO compared to other treatments.

Personalized Treatment Decisions:

- Develop protocols that take into account patient-specific factors like age, overall health, and lifestyle, which influence rEPO dosage decisions. This personalized approach can lead to better treatment outcomes.
- Promote care models that emphasize individualized treatment plans and regular monitoring, ensuring that adjustments to rEPO therapy are timely and based on comprehensive patient assessments.

Improving Patient Outcomes:

- Encourage a bi-weekly follow-up schedule for patients on rEPO therapy, as adopted by 50% of doctors, to ensure timely adjustments and monitoring of patient progress.
- Advocate for holistic management of anemia that includes iron supplementation for patients not responding to rEPO. This approach can help in addressing underlying deficiencies and improving overall treatment effectiveness.
- Implement systems to track patient outcomes systematically, which can provide valuable data to further refine treatment protocols and enhance patient care.

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