
بسم الله الرحمن الرحيم

ANEMIA & HEMODIALYSIS

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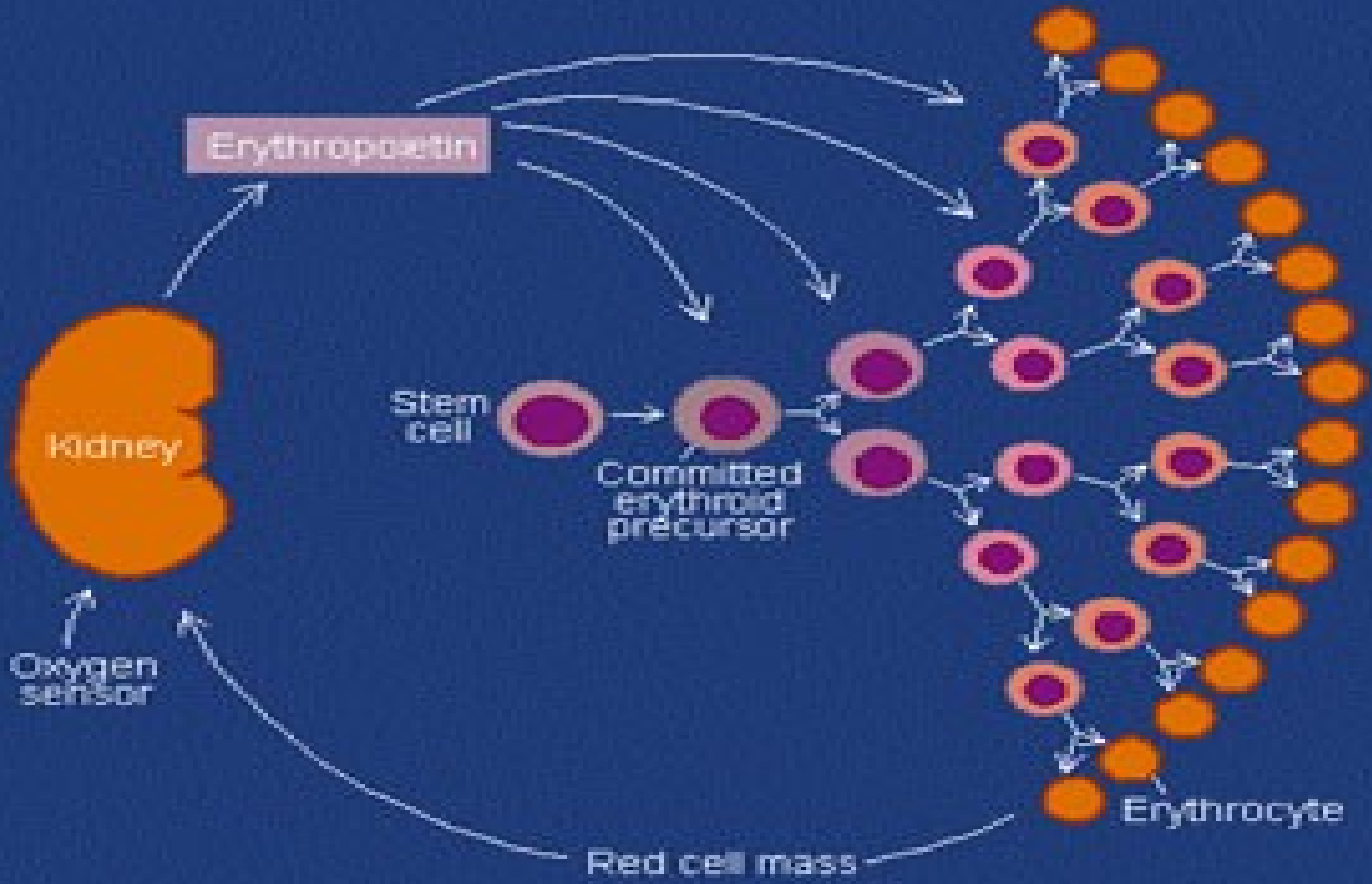
Anemia of CKD

- The anemia of **CKD** is, in most patients, normocytic and normochromic, and is due primarily to reduced production of erythropoietin by the kidney and to shortened red cell survival
- Anemia in those with CKD : begin when the Hgb level is less than 12 g/dL in females, and Hgb levels of less than 13.5 g/dL in adult males .
- Anemia becoming increasingly common as GFRs decline below 60 mL/min per 1.73 m2

Erythropoietin feedback loop



Anemia is associated with:

- Independent risk factor for development of LVH
- Independent risk factor for hospitalization (CV and non-CV related)
- Increased CV morbidity and mortality
- Poorer quality of life
- Higher relative risk for death than diabetes

Etiologic Classification of Anemia in CKD:

- hypoprolifrative anemia due to Epo deficiency
- Anemia due to :
  - Malnutrition & Malabsorption
  - iron deficiency
  - folate deficiency
  - Vit B12 deficiency
- Anemia due to Loss of blood in….
- AL toxicity
- Other disease: hyperparathyroidism, hypothyroid,….

Signs & symptoms of anemia

Target Hb & hct

Hgb: 11_12 mg/dl

Hct: 33_36%

Adverse effects for normal Hgb in hemodialysis patient

- Major adverse consequences with normal or near-normal Hgb levels include:
- **cerebrovascular events**,
- **arteriovenous access thrombosis**,
- **hypertension**.

OVERVIEW OF TREATMENT OPTIONS

1_ Red blood cell transfusions

Complications:

- *transfusion-transmitted infection,*
- *immunologic sensitization,*
- *iron overload syndromes,*
- *volume overload,*
- *transfusion reactions.*

2_ Androgens

3_ *Erythropoiesis-Stimulating* agents (ESAs):

***Erythropoiesis-Stimulating* agents (ESAs):**

Five ESAs are currently approved for treatment of anaemia in CKD patients:

- Epoetin Alfa (Eprex./Epogen./Procrit./Erypo.)
- Epoetin beta (NeoRecormon./Recormon.) Darbepoetin Alfa (Aranesp./Nespo.)
- Epoetin delta (Dynepo™)
- MIRCERA (methoxy polyethylene glycol-epoetin beta), the first and only continuous erythropoietin receptor activator.

OVERVIEW OF TREATMENT OPTIONS

recommended dosing schedules:

- For **epoetin alfa**, dosing is three times weekly IV and SC.
- For **epoetin beta**, dosing is once weekly SC to TIW IV and SC.
- For **darbepoetin alfa**, dosing is QW & Q2W IV and SC .
- **MIRCERA** :
- In both patients on dialysis and patients not on dialysis.
- can be administered either SC or IV.
- Q2W as a single IV or SC.
- well tolerated, with a safety profile
- Significant advantages for patients
- requires no refrigeration

Before treatment

- **Among patients with evidence of iron deficiency, iron supplements should be given first and iron deficiency corrected prior to initiating EPO.**
- ***hypertension* should be corrected before EPO therapy is begun.**

Erythropoietin

1- کنترل فشار خون بیمار قبل از تزریق (فشار خون سیستولیک < 160)
2- بررسی دارو: قبل از تزریق از نظر وجود ذرات یا تغییر رنگ
3- تکلن نادن دارو (ناتوره شدن گلیکو پروئین)
4- فقط برای یک بار مصرف – باقیمانده دور ریخته شود (فاقد ماده نگهدارنده)
روش مصرف: iv. Or s.c ؟
Half time in iv: 4-12 h
Half time in sc: 24 h
Dose of drug in s.c= 20%-40% iv dose

5- تزریق داخل وریدی طی حداقل 1-5 دقیقه – تزریق آهسته تر در بیمارانی واجد علائم شبه آنفولانزا – اجتناب از انفوزیون وریدی یا مخلوط با سایر داروها
6- تزریق زیر جلدی حداکثر حجم: 1 میلی لیتر – حجم های بیشتر در مکانهای دیگر – محل بازوها یا دیواره قدامی شکم – تغییر محل تزریق
7- رقیق نکردن دارو و عدم انتقال به ظرف دیگر

حفظ زنجیره سرد

ESAs Side effects:

- The most common side effects of EPO treatment:

- HTN 20 to 30 percent of patients
- headache (which occurs in 15 percent of cases)
- influenza-like syndrome (affecting 5 percent).
- The influenza-like syndrome is of unknown etiology, but is responsive to anti-inflammatory drugs

ESAs Side effects:

- Clotting : Hct<36%. ;Access thrombosis
- Hyperkalemia
- Seizures
- Pure Red Cell Aplasia
- LVH
- **Inadequate Response to Eprex**: 96% inadequate iron & dose of EPO….

ESA therapy & Hypertension

- Hypertension develops or worsens in 20–30% of renal patients
- occurs as early as 2 weeks or up to 4 months after the onset of therapy
  - Postulated mechanisms include increased viscosity,
  - an association between hematocrit & prevalence of hypertension
  - enhanced vascular reactivity due to the correction of hypoxia
  - vasoconstrictive responses due to the correction of anemia.
  - rHuEpo may lead to catecholamine release and activation of the renin–angiotensin system
  - rHuEpomay have a direct vasopressor effect due to SMC contraction at the level of the small resistance vasculature which may in part be due to a rise in intracellular calcium level

Smith K, Bleyer A et al. The cardiovascular effects of erythropoietin. Cardiovascular Research 2003 59(3); 538-548

PREVENTION AND TREATMENT HTN:

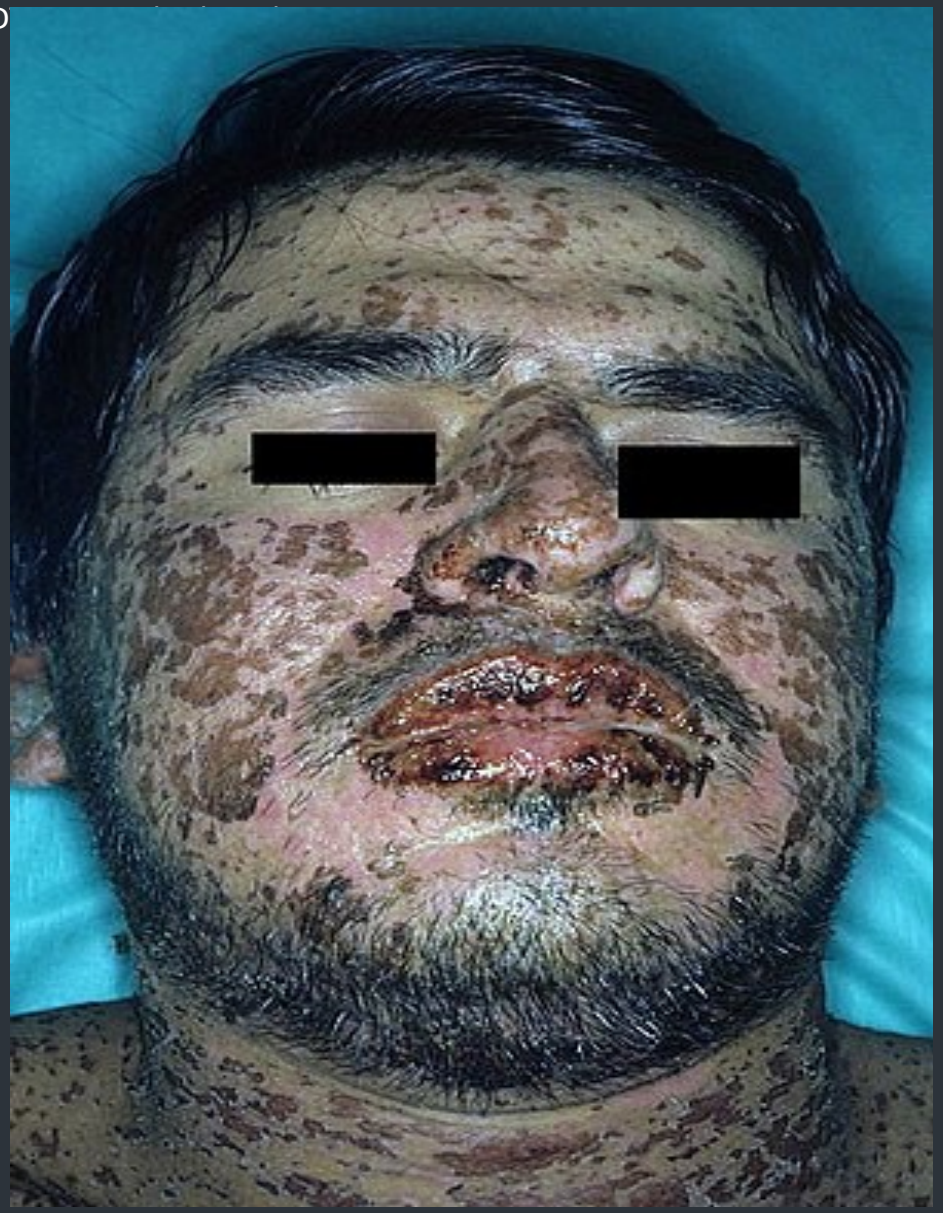
- BP must be monitored
- In comparison, the BP is less likely to rise after subcutaneous administration
- **Antiplatelet agents** : may reduce the risk of EPO-induced hypertension.
- **fluid removal** (via dialysis and the
- **administration of antihypertensive agents: first choice, Beta-adrenergic blockers** and **vasodilators** should be considered as agents of first choice, although calcium channel blockers and ACE inhibitors also may be effective.

- **European Medicines Agency:**
  - Risk of severe cutaneous adverse reactions Stevens-Johnson Syndrome (SJS) & Toxic-epidermal necrolysis (fatal)Class effect of all r-HuEPO
  - More severe with long acting r-HuEPO

SJS & TENS

- **SJS**–severe skin reaction.
- Less than 10% skin involved
- **TENS**–more than 30% skin involved
- Complications
- ***Dehydration***
- ***Sepsis***
- ***Pneumonia***
- ***Multi-organ failure***

Fresenius/ED



Severe Cutaneous Reactions

Signs & Symptoms Widespread rash with reddening & blistering of skin, oral mucosa, eyes, nose, throat, genital area
Follow flu like symptoms –fever, tiredness, muscle & joint pain
Peeling & shedding of skin that looks like a severe burn

top epoetin treatment immediately
Pain management, antihistamines, antibiotics, immunoglobulins/corticosteroids
Never to be given an r-HuEPO again

cause of EPO resistance:

- ***Iron deficiency***
- Bone disease due to secondary hyperparathyroidism
- Occult malignancy and unsuspected hematologic disorders
- MM /myelofibrosis /myelodysplastic syndrome
- Hemoglobinopathies
- The administration of ACE inhibitors and/or ARBs.
- Development of pure red cell aplasia associated with the presence of neutralizing anti-erythropoietin antibodies
- Presence of HIV infection
- Chronic inflammation :presence of a failed kidney transplant or an occult infection of an old nonfunctioning AV graft may underlie such inflammation in some patients
- accumulation of aluminum in bone

cause of EPO resistance:

- ***Iron deficiency*** **Major cause of EPO resistance 96%**
- In Hemodialysis population:
  - Losses of 3-9 mL of blood / 3-9 mg of iron/day due to Blood losses into the dialyzer, dialysis tubing, venipuncture

- Bennett L, Wittwer I, Judge P Managing anemia in pregnant women with CKD. Jouof Ren Nursing 2012; 4 (5); 24-28

Normal range

- Iron: 60-170 micg /dl
- TIBC: 230-440 micg /dl
- TSAT= (Iron/TIBC)100: 20-50 %
- Ferritin: 100-800 ng/ml

Considerations Before Administering Parenteral Iron

- Blood Pressure –what parameters?
- Infection
- History of allergy –drugs, food, base metals
- History of anaphylactoid reactions
- Co-morbidity –asthma, liver disease, rheumatoid arthritis, gout, eczema
- Pregnancy

Parenteral Iron and Infection:

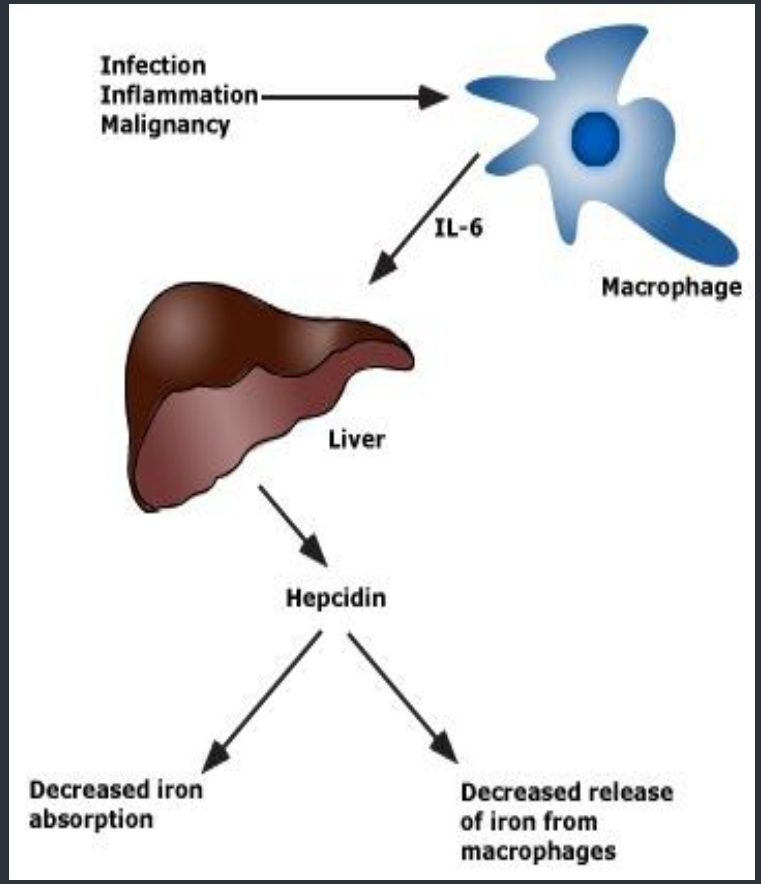
- Iron is essential for bacterial growth
- Free iron may enhance bacterial growth
- Some bacteria produce iron chelators to compete for iron
- Others acquire iron from transferrin by a membrane bound transferrin receptor
- In vitro & in vivo studies –excess iron ? impairs neutrophil & T-cell function impairing host resistance
- KDIGO guidelines –not to administer iron during active systemic infections

IschidaJH, Johansen KL Iron & Infection in HD patients SeminDial 2014;27:26-36

Fell LH, ZawadaAM et al Distinct immunologic effects of different IV iron preparations on monocytes. NDT 2014;29;809-822

Iron & the Inflammatory Process:

- Anaemia of chronic disease (ACD) associated with elevated cytokine levels
- Inflammatory cytokine IL-6 induces production of hepcidin in hepatocytes
- During inflammation, hepcidin restricts iron availability by regulating intestinal iron absorption and recycling by tissue macrophages
- A reduction in iron available for erythropoiesis results in ACD



- **Potential Side Effects of Parenteral Iron**
- **Anaphylactoid**
- **Anaphylactic**

Considerations after Parenteral Iron: Measuring Iron status

- Transferrin –Transferrin saturation (%)
  - TSAT undergoes circadian rhythm Blood for TSAT measurement should be taken in the morning
  - TSAT values from blood samples collected at different times of the day should not be compared

- HörlW et al NDT June 2007 Volume 22 Supplement 3

Not earlier than 1 week after receiving IV iron

- Routinely at intervals of:
- 4 weeks (during correction phase)
- up to 3 months (maintenance phase)

Considerations before Parenteral Iron
Measuring Iron status

توجهات پرستاری :

- روش کار را به بیمار توضیح دهید.
- قبل از اندازه گیری سطح اهن سرم باید از انتقال خون اجتناب نمود.
- از آنجاییکه سطح آهن سرم در طی روز تغییرات شدیدی دارد ترجیحا خونگیری صبح انجام شود
- از همولیز نمونه خودداری شود
- جهت اندازه گیری اهن سرم 12 ساعت ناشتایی الزامی است.
- از مصرف گوشت و منابع آهن در طی روز گذشته خودداری شود.
- در صورتیکه به میزان هموگلوبین هدف نرسیده اید و بیمار تحت درمان با اهن وریدی است . هرماه مقادیر اهن ارزیابی میشود
- در صورت رسیدن به میزان هدف مقادیر خونی هر ۳ماه یکبار کنترل میشود

- بهترین زمان چک پروفایل آهن به فاصله حداقل یک هفته از دریافت آخرین دوز آهن تزریقی می باشد.

Considerations before administering parenteral iron

- آهن وریدی یا خوراکی؟
- درمان با اهن خوراکی در بیمارانی درمراحل پیش از دیالیز یا دربیماران صفاقی موثر واقع میشود ولی در بیماران دیالیزی اهن وریدی در اصلاح مقادیر اهن خون موثر است.
- در نوبت اول استفاده از اهن تا 60 دقیقه بیمار را از نظر بروز عوارض و حساسیت تحت نظر بگیرید.
- شایع ترین علت عدم پاسخ به درمان با اریترو پویتین نا کافی بودن آهن می باشد.
- در تمام انواع آهن وریدی ریسک واکنش های حاد شامل تنگی نفس، کاهش فشار (در صورت تزریق سریع)، واکنشهای پوستی، تهوع و استفراغ و واکنش های آنافیلاکتویید و آنافیلاکسی وجود دارد.
- با توجه به واکنش های حاد انافیلاکتیک(1%)، حتط هنگام تزریق آهن وریدی،امکان دسترسی به وسایل احیا و در دسترس باشد
- توجه شود ونوفر نیازی به نگهداری در یخچال ندارد.
- با توجه به انواع اهن تزریقی جهت استفاده به دستور پزشک و دستورالعمل دارو مراجعه.

Parenteral Iron

- Amp venofer: 5cc – 100 mg sucrose iron

- IV: without dilution
  1cc/1min
  test dose: 1cc in 1-2 min, then after15 min don’t reaction
- Infusion: 5cc venofer immediately before infusion+20cc Nacl 0.9%
  each 100 mg in 15 min
  test dose:20 mg/15 min
- Intra dialysis set: the same iv

Future Treatment Options for CKD-Related Anemia

- Continuous erythropoiesis receptor activator (CERA) – not FDA Approved

  SC or IV dosing up to 4-week interval

- Erythropoietin-mimetic peptides

  long duration of action that allows for once monthly dosing

- Hypoxia-Inducible Factor Stabilizer

  First oral therapy for the treatment of anemia in CKD

Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitors (HIF-PHIs

- 4 companies developing a new class of drug -molecules that stimulate erythropoiesis by inhibition of HIF –prolyl hydroxylase enzymes
- By stabilizing the HIF complex it stimulates components of natural response to hypoxia
- Clinical data shows Stimulates endogenous EPO production
- Reduces circulating hepcidin concentrations in those with CKD thus improving availability of iron

Gupta N, Wish JB Am J Kidney Dis 2017 Ju

HIF-Prolyl Hydroxylase Inhibitors

Advantages:

- Oral medications
- No cold chain
- Induce considerably lower but more consistent blood EPO levels therefore potentially fewer adverse cardiovascular effects at comparable Hb levels
- No rhEPO induced hypertension

Disadvantages

- Potential for switching on/stimulating other genes in the sequence, in particular VEGF
- Tumor growth

Conclusion

Anaemia treatment in CKD usually involves the use of drugs
Many drugs are widely used but should never be used complacently
All drugs have potential for adverse reactions and the consequences for each individual should be weighed up.
Patients should be informed of risks vs benefits for consent to be meaningful and legal. They should feel able to refuse treatment without prejudice to other treatments
All HCP involved in prescribing, dispensing, administering have a responsibility to remained informed themselves in regard to pharmacokinetics, pharmacodynamics & drug interactions to be a patient advocate and prioritise patient safety

- خانمی48 ساله که بمدت 6 سال تحت درمان با همودیالیز با دستور زیر قرار دارد :

3/w, Dialyzer with kOA>1200, 4hour. KT/V=1.56

- تحت درمان با اپرکس،4000واحد، سه بار در هفته
- ونوفر100 میلی گرم ماهی یکبار
- سینا کلست 30میلی در روز و...
- برخی از ازمایشات و داروهای مصرفی بیمار در ذیل قید شده است .گمان میکنید علت آنمی وی چه میباشد

تیر: شهریور.

Hb =10.2. Hb9 .

- Ca=8.5 ca=6.9
- P=4 p= 4
- ALP=800 ALP= 1655
- PTH=1040 PTH=2450
- Fe=58, TIBC=200,Ferritin=495