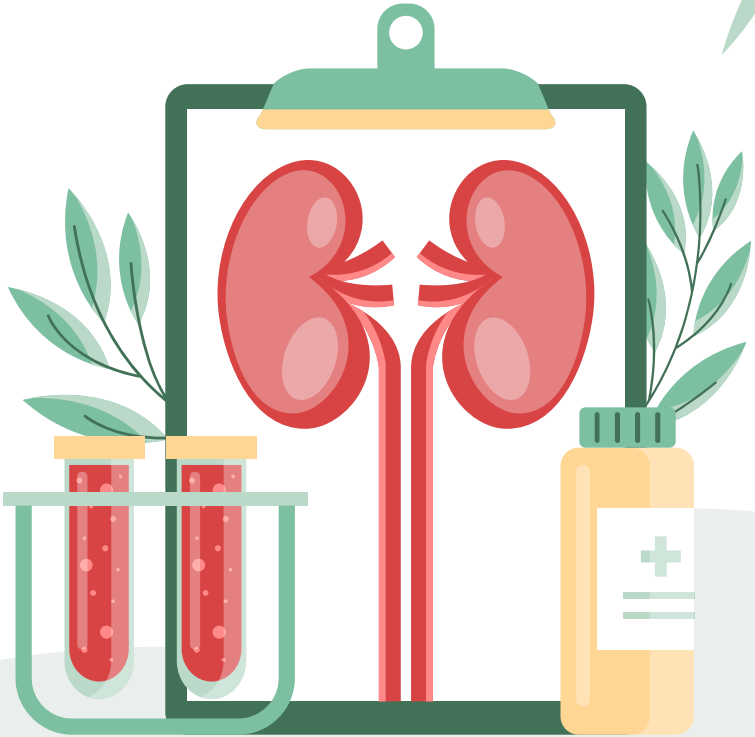
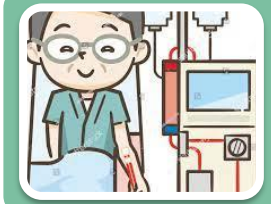
Laboratory Monitoring for Dialysis Management



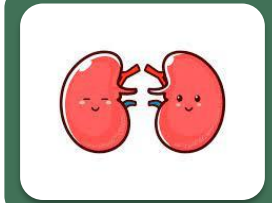
Ira Puspitawati
KSM Patologi Klinik dan Kedokteran Laboratorium
RSUP Dr Sardjito Yogyakarta

Laboratory Monitoring for Dialysis Management



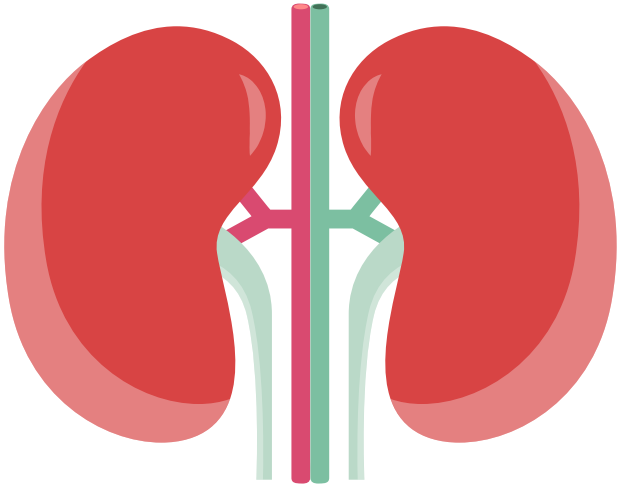
To ensure dialysis adequacy

To detect Complication of CKD Stage 5



To Predict Prognosis of CKD Stage 5

Dialysis



01

Hemodialysis

Hemodialysis is a procedure where **a dialysis machine** and a special filter called an artificial kidney, or a dialyzer, are used to clean the blood.

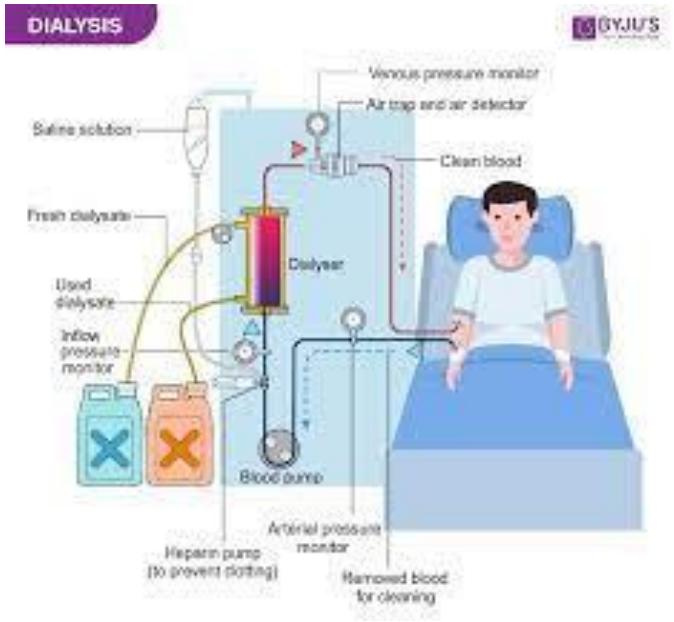
02

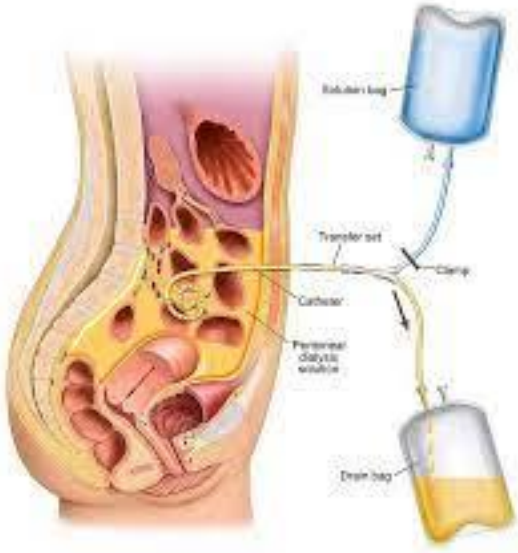
Peritoneal Dialysis

Peritoneal dialysis uses the lining on the inside of the abdomen as a natural filter for blood.

https://www.kidney.org/atoz/content/hemodialysis

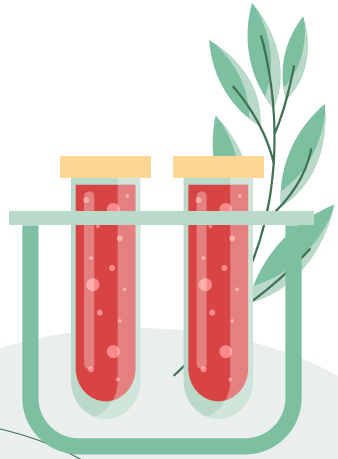
Hemodyalisis vs Pertoneal Dialysis



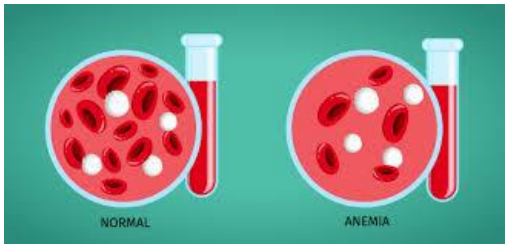


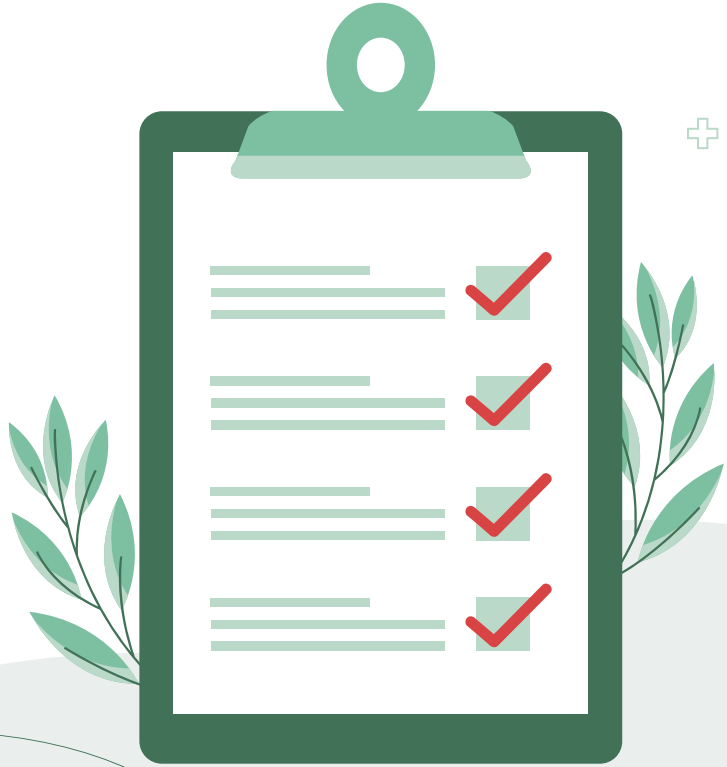
Complications of CKD stage V

- Anemia
- CKD-Bone Mineral Dissorder
- Cardiovascular Disease
- Infection



Anemia in CKD





Pathophysiology Anemia of CKD

- Anemia of CKD is a **multifactorial process** due to relative EPO deficiency, uremic- induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis.
- Recent work has identified hepcidin excess as a main contributor to the **disordered iron homeostasis** and anemia of CKD by **impairing dietary iron absorption and iron mobilization from body stores** (Babbit, et al, 2012)

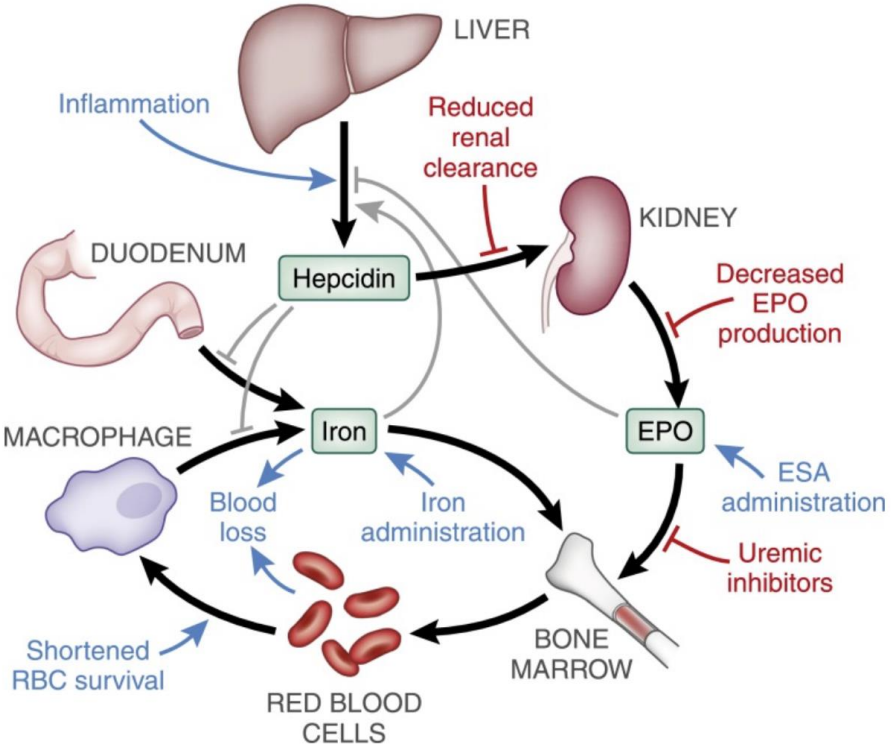
Babbit, JL, Lin HY. J Am Soc Nephrol. 2012

Pathophysiology Anemia of CKD

- CKD patients **have functional iron deficiency** →impaired iron release from body stores → unable to meet the demand for erythropoiesis (also called reticuloendothelial cell iron blockade) → **low serum transferrin saturation** and normal or high serum ferritin (a marker of body iron stores) (KDOQI, 2006).
- **Hepcidin** is the main hormone responsible for maintaining systemic iron homeostasis.
  - induces degradation of the iron exporter, ferroportin, on duodenal enterocytes, reticuloendothelial macrophages, and hepatocytes → **inhibit iron entry into the plasma**
  - Inflammatory cytokine induce Hepcidin secretion

KDOQI. *Am J Kidney Dis* 47[Suppl 3]: S11–S145, 2006 [PubMed: 16678659
Nemeth, et al. *Science* 306: 2090–2093, 2004

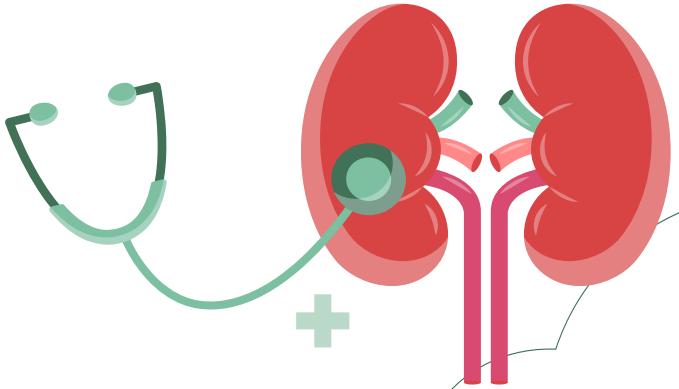
Pathophysiology Anemia of CKD



Anemia in CKD

Definitions

1. Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is < 13.0 g/dL in males and <12.0 g/dl in females.
2. Diagnose anemia in children with CKD if Hb concentration is < 11.0 g/dL in children 0.5-5 years, <11.5 g/dL in children 5-12 years, and < 12.0 g/dL in children 12-15 years.



Laboratory Monitoring of Anemia in CKD

Complete blood count

- Provides information about the **severity of anemia** and **adequacy** of bone marrow function
- The anemia of CKD is **hypoproliferative, and in general, normochromic and normocytic**.

Kidney International Supplements (2012) 2, 288–291

Laboratory Monitoring of Anemia in CKD

Iron Status

- To asses the **presence or absence of** storage iron and the **availability** of iron to support ongoing erythropoiesis.
- **The serum ferritin** is the **most commonly** used test for **evaluation of storage iron → acute phase reactan and is affected by inflammation.**
- ‘Gold standard’ remains examination of a bone marrow aspiration stained for iron.
- **The transferrin saturation (TSAT)**→ the most commonly used measure of the **availability of iron** to support erythropoiesis

Kidney International Supplements (2012) 2, 288–291

Laboratory Monitoring of Anemia in CKD

Iron Status

- **Serum ferritin values < 30 ng/ml** → indicate **severe** iron deficiency are highly predictive of **absent iron stores** in bone marrow.
- Most CKD patients, including those who are on HD, will have **normal** bone marrow iron stores when their **serum ferritin level is ≥300ng/ml .**
- Other tests of iron status, such as percentage of **hypochromic RBC** and **reticulocyte Hb content** may be used instead of, or in addition to.

Kidney International Supplements (2012) 2, 288–291

Laboratory Monitoring of Anemia in CKD

Vit B12 and folic acid

- Folate and vitamin B12 deficiency are uncommon but important causes of treatable anemia, typically associated with macrocytic red blood cell (RBC) indices.
- A prevalence of vitamin B12 and folate deficiency in <10% of HD patients

Additional tests

- Addition to those indicated above, may be appropriate in individual patients and in certain specific clinical settings
- Ex: **High sensitivity C-reactive protein (CRP)** → if occult inflammation is a concern

Kidney International Supplements (2012) 2, 288–291

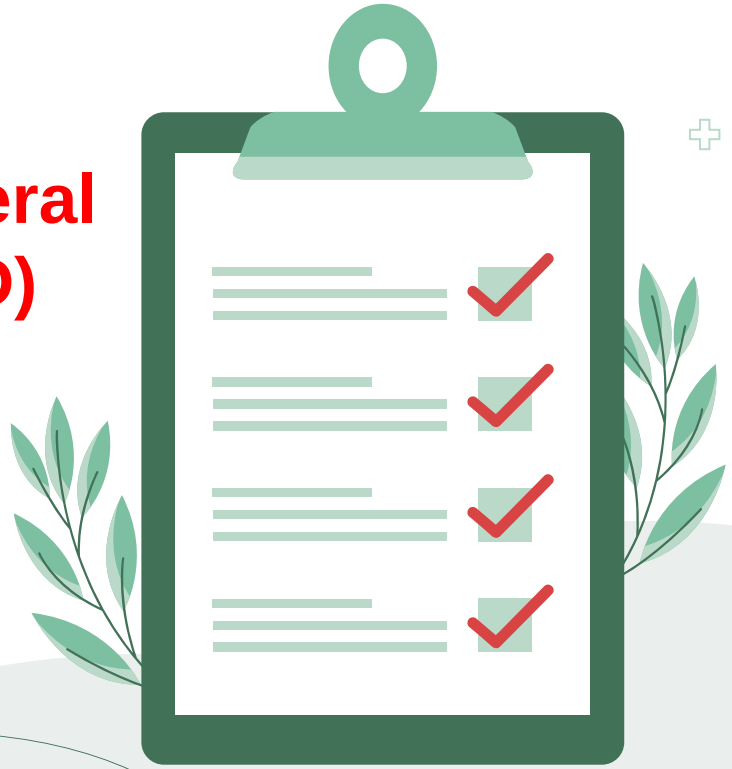
Laboratory Monitoring of Anemia in CKD

Frequency of Testing

- **For CKD patients without anemia**
  At least every 3 months in patients with CKD 5HD and CKD 5PD.
- **For CKD patients with anemia** not being treated or with an ESA, measure Hb concentration when clinically indicated and at least every 3 months in patients with CKD 5ND and CKD 5PD at least monthly in patients with CKD 5HD .

Kidney International Supplements (2012) 2, 288–291

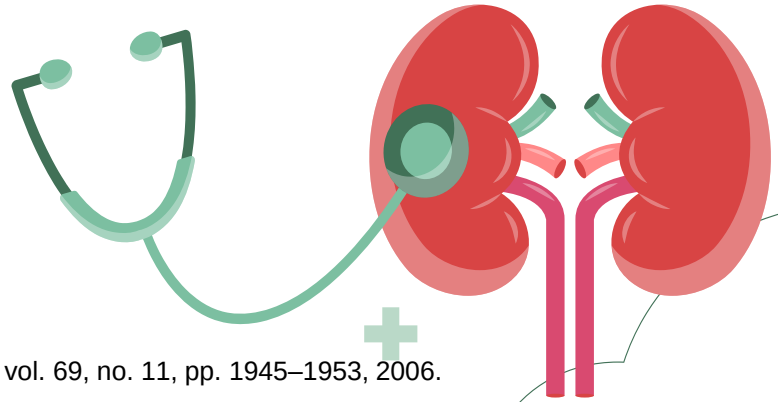
Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)



Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

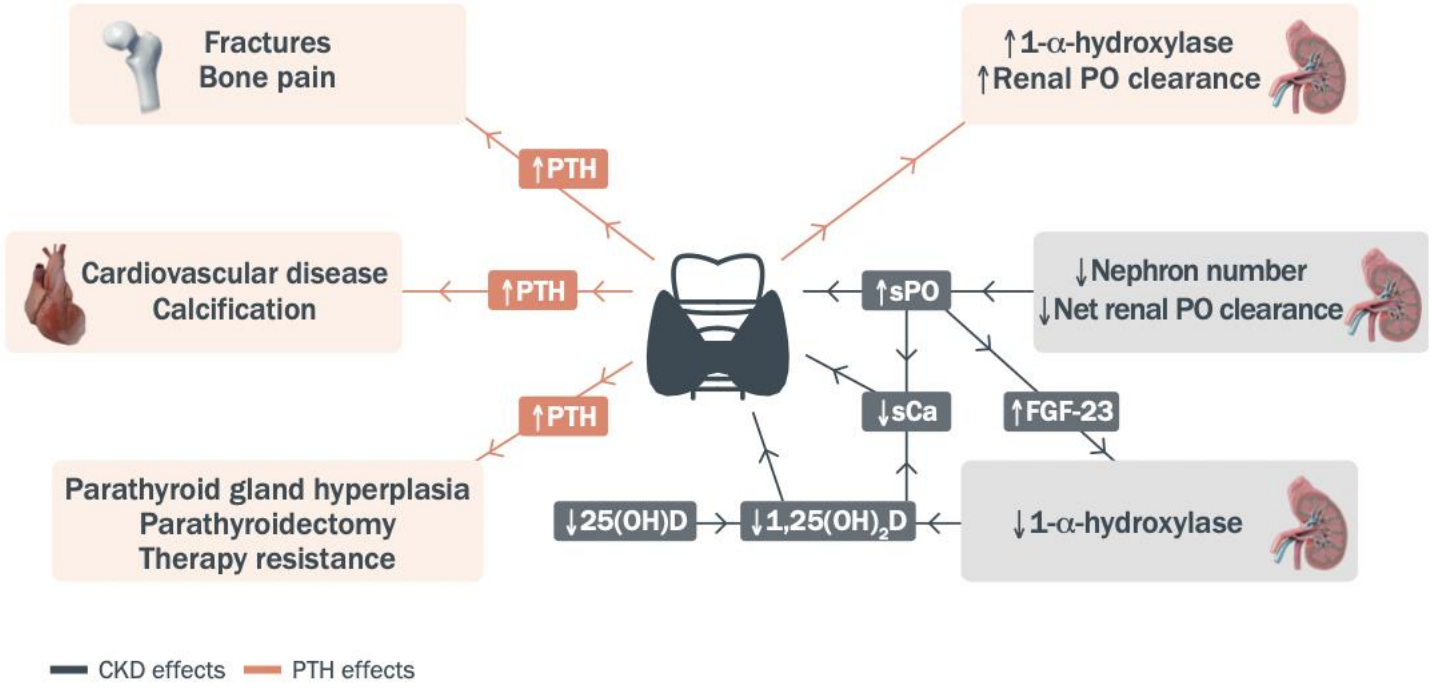
Definitions

- A KDIGO position statement published in 2006 defined CKD-MBD disease as due to either one or a combination of the following clinical situations: (a) abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; (b) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; (c) vascular or other soft tissue calcification



S. Moe et al. Kidney International, vol. 69, no. 11, pp. 1945–1953, 2006.

Pathophysiology CKD-MBD



Adapted from Cunningham J et al. 2011,[2] Rodriguez M et al. 2005,[3] Friedl C et al. 2017[5] and Wu W et al. 2018.[6]
FGF-23: Fibroblast growth factor-23; PO: Phosphate; PTH: Parathyroid hormone; sCa: Serum calcium; sPO: Serum phosphate; 25(OH)D: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D.

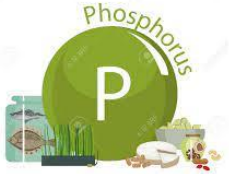
Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Vascular and Bone Abnormalities

- A relationship between bone and vessels predisposing to the formation of vascular and soft tissue calcifications in CKD-MBD patients
- **Hyperphosphatemia** → activate a sodium-phosphate cotransporter → increase in intracellular phosphorus concentration in vascular smooth muscle cells→ production of the *core-binding factor alpha-1* (a transcription factor for osteoblastic differentiation of smooth muscle cells) → triggering an active vascular ossification process (Jono, *et al*, 2000)
- **Hyperphosphatemia** → progressive coronary calcification in CKD patients. Vascular stiffness → elevated mortality in patients (Blacher, *et al,* 2001).

Jono, et al. Circulation research, vol. 87, no. 7, pp. E10–E17, 2000
J. Blacher, *et al.* Hypertension, vol. 38, no. 4, pp. 938–942, 2001.

Laboratory Monitoring of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)



Serum Phosphorus

- **Higher levels of serum phosphorus**, even within the normal range, are associated with increased cardiovascular morbility and mortality (Dhingra, *et al* 2017).

Serum Calcium

- **Calcium levels >9.5 mg/dL** or even higher are associated with increased mortality in CKD patients (Tentory, *et al*, 2008).
- However, **low serum calcium** levels were associated with increased mortality in time-varying analyses and in combination with higher serum phosphorus (>3.5 mg/dL) and PTH levels (>150 pg/mL) (Kovesdye, *et al,* 2010)

F. Tentori, et al. American Journal of Kidney Diseases, vol. 52, no. 3, pp. 519–530, 2008
R. Dhingra, et al. Archives of Internal Medicine, vol. 167, no. 9, pp. 879–885, 2007
C. P. Kovesdy, et al," Clinical Journal of the American Society of Nephrology, vol. 5, no. 3, pp.468–476, 2010

Laboratory Monitoring of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Serum PTH

- In a large observational study, only intact PTH levels higher than 600 pg/mL were associated with an increased mortality risk (Block, *et al*, 2004).

Serum Vitamin D

- In patients with stages 3–5D, the KDIGO guidelines → measuring circulating levels of 25 VD and repeating testing at intervals determined by the baseline values obtained

G. A. Block, et al. Journal of the American Society of Nephrology, vol. 15, no. 8, pp. 2208–2218, 2004.

Laboratory Monitoring of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Alkaline Phosphatase

- To provide additional information on bone turnover (with PTH levels).
- Recent studies showing the association between total alkaline phosphatase levels and mortality in CKD and ESRD patients (Kovesdy, *et al* 2010)

C. P. Kovesdy, et al. Nephrology Dialysis Transplantation, vol. 25, no. 9, pp. 3003–3011, 2010.

Laboratory Monitoring CKD-MBD

CKD Stages 3-5 and Dialysis (D)

	BIOCHEMICAL COMPONENTS				BONE			BLOOD VESSELS
CKD STAGE (GFR IN mL/ min/1.73 m²)	**Ca,P**	**PTH**	**ALP**	**25(OH)D**	**BONE-SPECIFIC ALP**	**BONE BIOPSY**	**BMD**	**CALCIFICATION**
Stage 3 (30–59)	Once (1C);§ then every 6 – 12 months (NG)*	Once (1C);§ then based on level and CKD progression (NG)	Once (1C) §	Once (2C); then based on level and treat-ments (2C)	Can be used to evaluate bone disease (2B)	In various settings and before treatment with bisphospho-nates (NG)	No routine testing in presence of CKD-MBD (2B)	Routine screening not recommended
Stage 4 (15–29)	Every 3 – 6 months (NG)	Every 6 – 12 months (NG)	Every 12 months†† (NG)					
Stage 5 (<15 or dialysis)	Every 1 – 3 months (NG)	Every 3 – 6 months (NG)						

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int*. 2009;76 (suppl 113): S1-S130. Available at **www.kdigo.org**

Laboratory Monitoring of CKD-MBD

Table 2: KDIGO guideline for CKD-MBD: laboratory target range.

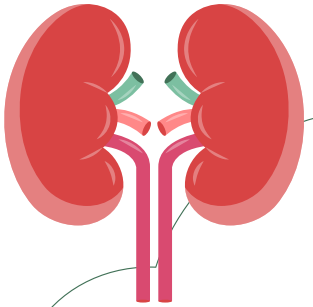
CKD stage (mL/min)	PTH target	
	KDOQI	KDIGO
3 (59–30)	25–70	
4 (29–15)	70–110	Unknown
5 (<15)	150–300	
5D (dialysis)		In the range of 2–9 times the upper reference limit for the assay without marked changes over time
CKD stage (mL/min)	Phosphorus target (mg/dL)	
	KDOQI	KDIGO
3 (59–30)	2.7–4.6	
4 (29–15)		In the reference range
5 (<15)	3.5–5.5	
5D (dialysis)		Toward the reference range
CKD stage (mL/min)	Calcium target	
	KDOQI	KDIGO
3 (59–30)	In the reference range	
4 (29–15)		In the reference range
5 (<15)	8.4–9.5 (10.2)	
5D (dialysis)		

Cardiovascular Disease in CKD

Cardiovascular Disease in CKD

- CKD promotes CVD at an accelerated rate.
- People with CKD are more likely to experience **a cardiovascular event** than to progress to ESRD, have a worse prognosis with higher **mortality** after acute myocardial infarction (MI), and have a higher risk of **recurrent** MI, heart failure and sudden cardiac death.
- Population-based studies → an increased risk of death and cardiovascular mortality as **GFR falls below 60 ml/min/1.73** m2 or when **albumin is detected on urinalysis.**

KDIGO, Kidney International Supplements (2013) 3, 91–111



Laboratory Monitoring of Cardiovascular disease

BNP and NT-proBNP levels

- **The stimulus** for secretion of these biomarkers:
  - The hemodynamic load (i.e., myocardial stretch)
  - Severity of CHF and the degree of left ventricular dysfunction.
- NT-proBNP may have analytical advantages over BNP → **greater stability** due to a **longer half-life** (Mueller, et al, 2005)
- When the **eGFR is less than 60 ml/min/1.73 m²** → the accuracy of plasma BNP and NT-proBNP levels for detection and stratification of CHF becomes unreliable.
- **Heart failure and renal dysfunction** act synergistically → increase the secretion rates of BNP and NT-proBNP. In addition, decreased renal function reduces the clearance of BNP and NT-proBNP (Srisawasdi, *et al* 2010).

Mueller C, et al. Kidney Int 2005; 67: 278–284.
Srisawasdi, et al. Am J Clin Pathol 2010;133:14-23

Laboratory Monitoring of Cardiovascular disease

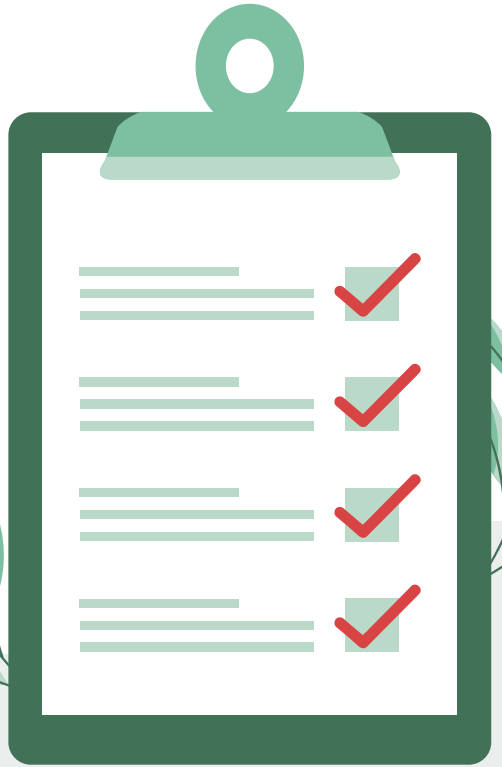
Troponin

- Cardiac troponins have proven to be specific markers of myocardial damage.
- In people with GFR <60 ml/min/1.73 m2 (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome (KDIGO, 2012)
- On people with ESRD where increases in serum cTnT concentrations have been observed in 20%–90% of subjects but generally much lower when cTnI was measured (Lamb, *et al*, 2004).

KDIGO, Kidney International Supplements (2013) 3, 91–111
Lamb EJ, et al. Ann Clin Biochem 2004; 41: 1–9.

Dialysis-associated Infection

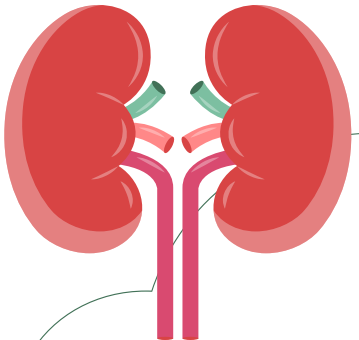
- **Peritoneal dialysis (PD)-associated peritonitis**
- **Hepatitis B and C**



Peritoneal dialysis (PD)-associated peritonitis

Diagnosis:

- Peritonitis should be diagnosed when at least two of the following are present:
  1) clinical features consistent with peritonitis, that is, abdominal pain and/or cloudy dialysis effluent;
  2) dialysis effluent white cell count > 100/μL or > $0.1.10^9$/L (after a dwell time of at least 2 h), with > 50% polymorphonuclear leukocytes (PMN);
  3) positive dialysis effluent culture (1C).



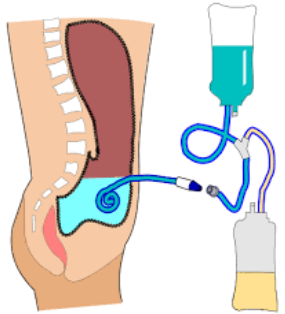
Philip, *et al*. Peritoneal Dialysis International 2022, Vol. 42(2) 110–153

Laboratory Evaluation of PD-associated peritonitis

Evaluation of PD Effluent

Cell count, differential of PD Effluent

- An effluent cell count with WBC > 100/μL (after a dwell time of at least 2 h), with > 50% PMN, is highly suggestive of peritonitis (Flanigan, et al, 1985).
- For patients on **Automated Peritoneal Dialysis** → the clinician should use the percentage of PMN rather than the absolute WBC count to diagnose peritonitis, and a proportion above 50% PMN is strong evidence of peritonitis, even if the absolute WBC count is less than 100/uL.



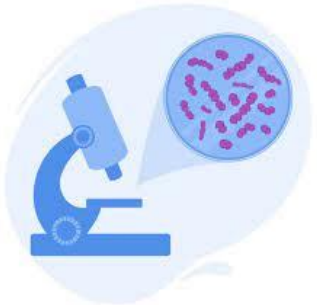
Flanigan MJ, *et al*.. Am J Kidney Dis 1985; 6(6): 420–424.

Laboratory Evaluation of PD-associated peritonitis

Evaluation of PD Effluent

Gram Stain

- Gram stain of the PD effluent should be performed even though the result is often negative (Buchanan, *et al*, 2019).
- An additional benefit of Gram stain is its effectiveness in early detection of fungal elements (de Filter, *et al*, 2019).
- The diagnostic yield of the Gram stain is increased if it is performed on a centrifuged specimen (Tanratananon, et al, 2021)



Buchanan, *et al*. Perit Dial Int 2019; 39(2): 190–192.
de Fijter, et al. . Perit Dial Int 2019; 39(6):574–575
Tanratananon, et al. Ann Med Surg (Lond) 2021; 63: 102139

Laboratory Evaluation of PD-associated peritonitis

Evaluation of PD Effluent

PD Effluent Culture

- Recommendation using the blood culture bottle(s) technique for bacterial culture of PD effluent.
- Sampling and culture methods be reviewed and improved if more than 15% of peritonitis episodes are culture negative
- Centrifugation of 50 mL PD effluent at 3000 g for 15 min, followed by resuspension of the sediment in 3–5 mL supernatant and inoculation on solid culture media or standard blood-culture media, increases the yield by **5–10 times** (Tanratananon, *et al*, 2021).

Tanratananon, et al. Ann Med Surg (Lond) 2021; 63: 102139

Laboratory Monitoring of Hepatitis in Dialysis Patient

Hepatitis C

- Screening patients with CKD for hepatitis C virus (HCV) infection.
- Follow-up HCV screening of in-center hemodialysis patients using immunoassay or NAT → report → New HCV infection → all patients be tested for HCV infection.
- Patients with resolved HCV infection → repeat testing every 6 months using NAT to detect possible re-infection.
- **Serum alanine aminotransferase (ALT)** level checked upon initiation of in-center hemodialysis and checked monthly.
- Assessing HCV-infected patients with CKD for liver fibrosis.

KDIGO 2022. Kidney International (2022) 102 (Suppl 6S), S129–S205 S153

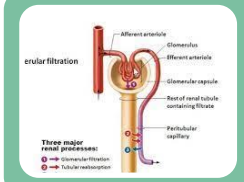
Laboratory Monitoring of Hepatitis in Dialysis Patient

Hepatitis B

- All patients starting haemodialysis should be known to be plasma HBV surface antigen (HBsAg) negative before having dialysis on the main dialysis unit.
- Patients on regular hospital haemodialysis who are immune to hepatitis B immunisation (anti HBs antibody titre > 100 mIU/ml), only need to be tested for HBsAg every 6 months.
- Nonresponders should be tested at least every 3months. For ease units may prefer to routinely test for **HBsAg every 3 months for all patients.**

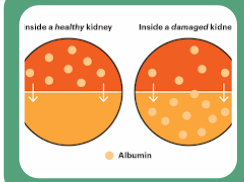
Garthwaite et al. BMC Nephrology (2019) 20:388

Laboratory Monitoring for Predicting Prognosis of CKD Std V



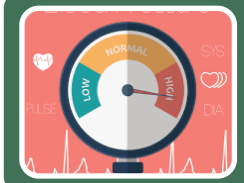
Glomerular Filtration Rate

- eGFR



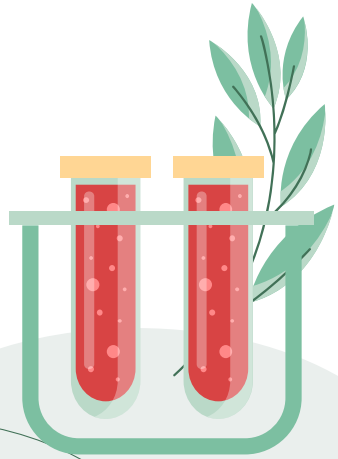
Albuminuria

- Albumin creatinine ratio (ACR)
- Albumine excretion rate



Other measures

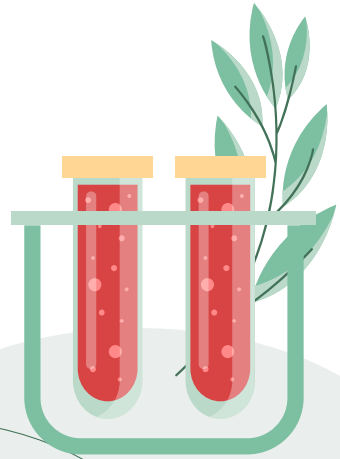
- Hypertension, DM
- Age, race



Predicting Prognosis of CKD Std V

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).



Neither the category of GFR nor the category of albuminuria alone→ prognosis for CKD patient.

Evaluation of GFR

1.4.3: Evaluation of GFR

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (*1A*)

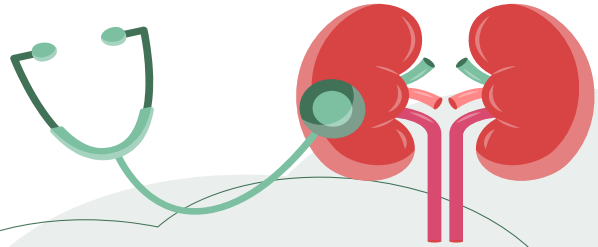
1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (*2B*)

1.4.3.3: We recommend that clinicians (*1B*):

- use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.
- understand clinical settings in which $eGFR_{creat}$ is less accurate.

1.4.3.4: We recommend that clinical laboratories should (*1B*):

- measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.
- report $eGFR_{creat}$ in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting $eGFR_{creat}$.
- report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.



Evaluation of Albuminuria

1.4.4: Evaluation of albuminuria

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (*2B*):

1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. (*1B*)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

Evaluation of Albuminuria

1.4.4.3: Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Graded*):

- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.
- Confirm ACR $\geq$ 30 mg/g ($\geq$ 3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.
- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

1.4.4.4: If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., α_1-microglobulin, monoclonal heavy or light chains, [known in some countries as "Bence Jones" proteins]). (*Not Graded*)

Evaluation of Albuminuria

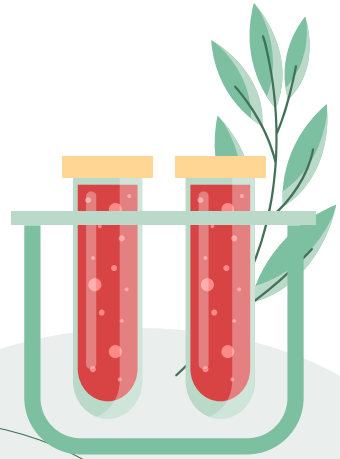
Table 6 | Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

Conclusions

- Aim of Laboratory monitoring in Dialysis patients are to asses the adequacy of Dialysis, to To detect Complication and To Predict Prognosis of CKD Stage 5.
- Some complication related with dialysis are anemia, CKD-MBD, Cardiovascular, Infection.
- Some consideration are needed to interprete the normal range of those laboratories results, related with the decrease of renal function.
- Laboratory monitoring should performed routinely based on guidelines.



Thank you