Anemia

- **90% of patients with CKD develop anemia**
- **Decreased renal mass - decreased or absent erythropoietin synthesis**
- **Decreased red cell production and secretion by the bone marrow**
- **Normochromic, normocytic, low reticulocyte count**
- **At GFR <40 ml/min Hct decreases in proportion to CKD, until the value 20% - 25% with ESRD**
- **Patients with polycystic kidney disease tend to have a higher Hct level relative to stage of renal failure**

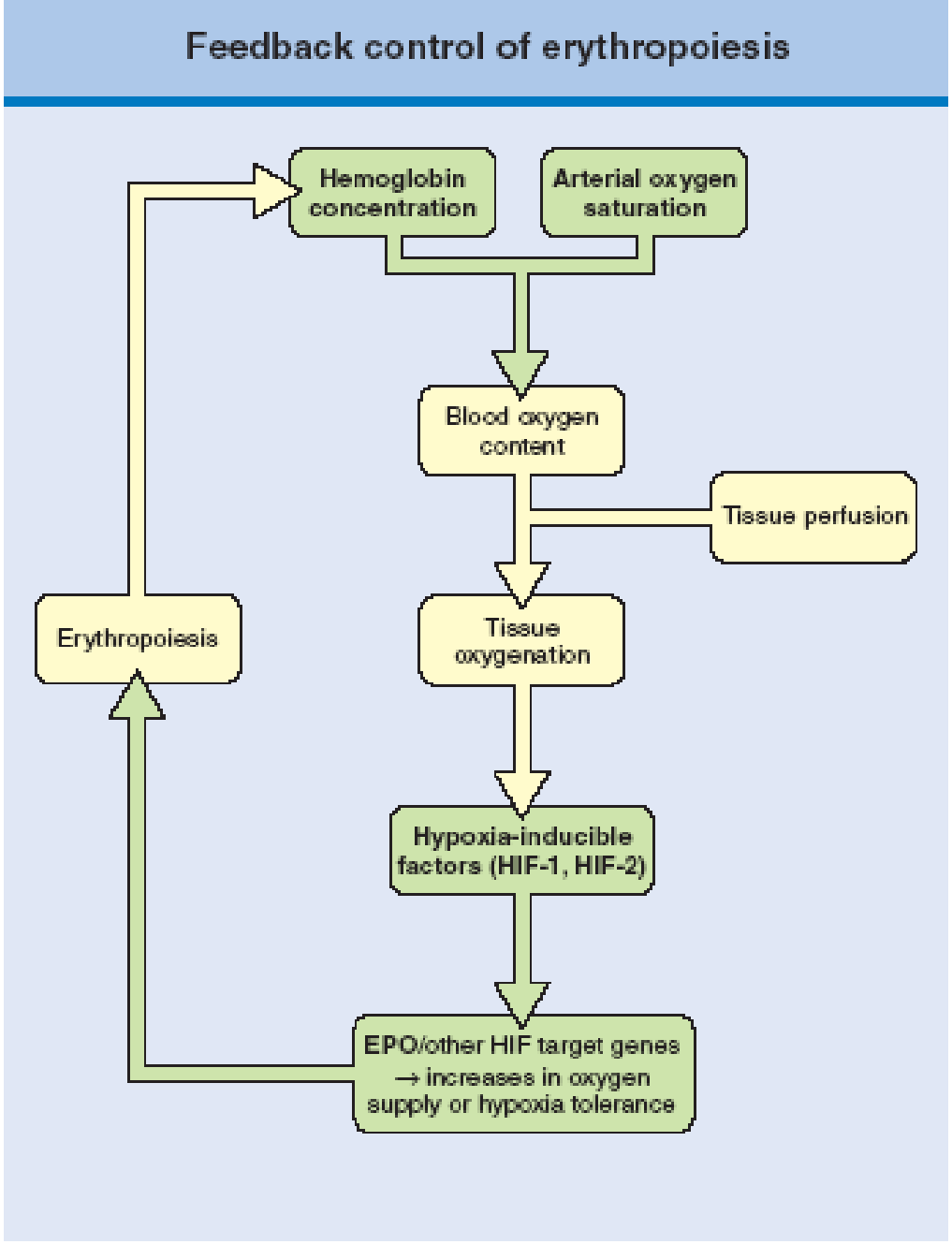


Figure 72.1 Feedback control of erythropoiesis.

Figure 72.2 Relationship between hemoglobin (Hb) and estimated glomerular filtration rate (GFR). Data are from a cross-sectional survey of individuals randomly selected from the general U.S. population (NHANES III). Results and 95% confidence interval are shown for males (*a*) and females (*b*) at each estimated GFR interval.

(From McClellan W, Aronoff SL, Bolton WK, et al: The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:501–510.)

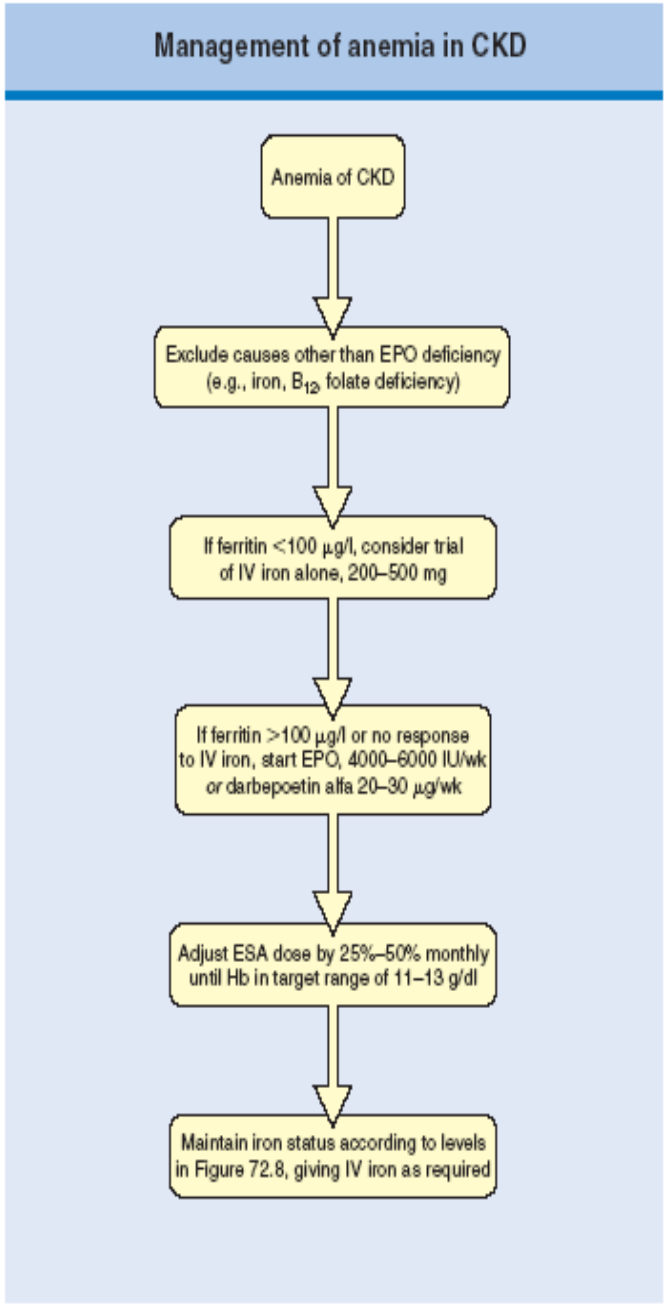
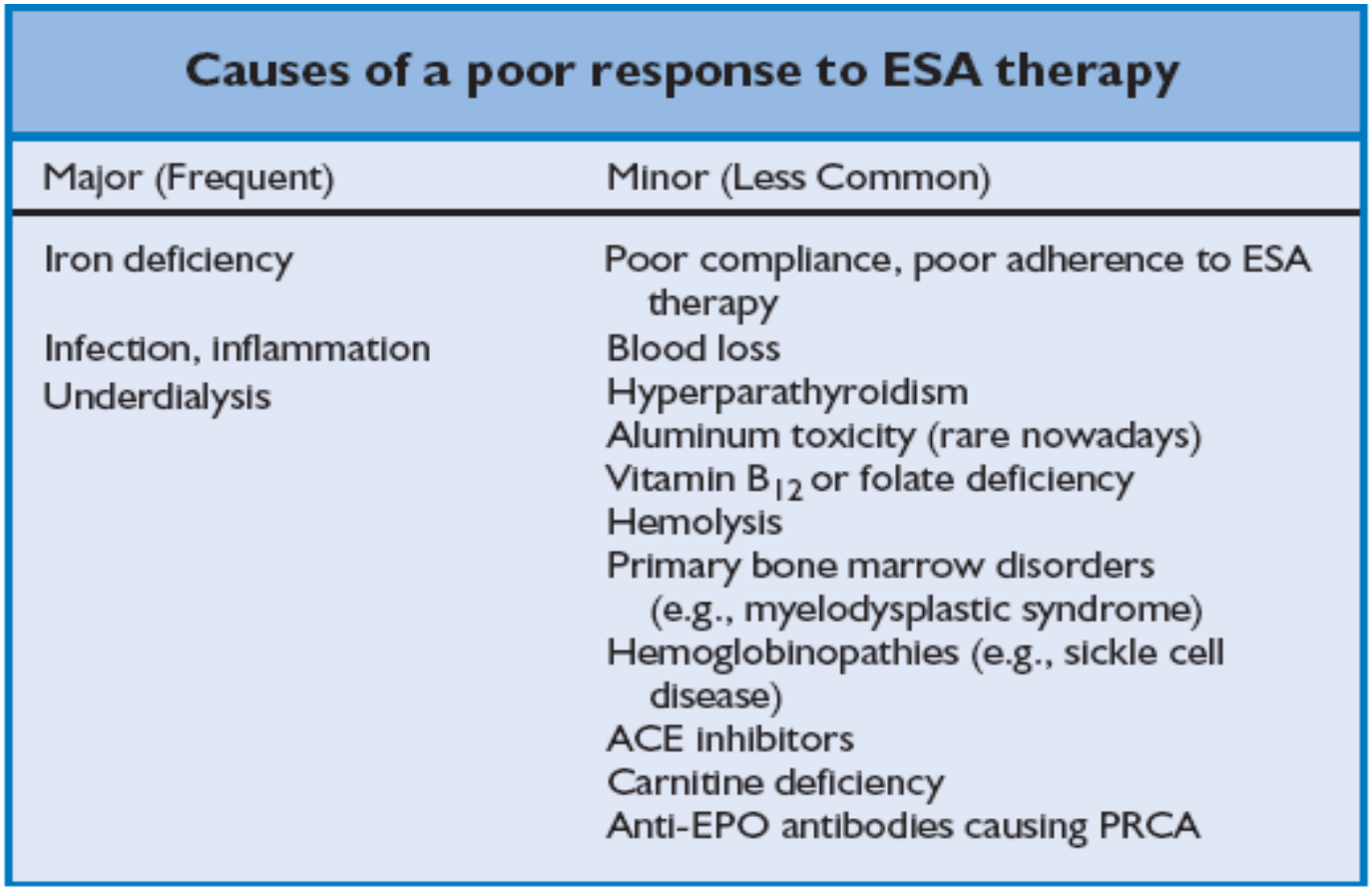


Figure 72.6 Management of anemia in patients with chronic kidney disease (CKD). EPO, erythropoietin; ESA,



Causes of a poor response to ESA therapy

Major (Frequent)	Minor (Less Common)
Iron deficiency	Poor compliance, poor adherence to ESA therapy
Infection, inflammation	Blood loss
Underdialysis	Hyperparathyroidism
	Aluminum toxicity (rare nowadays)
	Vitamin B_{12} or folate deficiency
	Hemolysis
	Primary bone marrow disorders (e.g., myelodysplastic syndrome)
	Hemoglobinopathies (e.g., sickle cell disease)
	ACE inhibitors
	Carnitine deficiency
	Anti-EPO antibodies causing PRCA

Figure 72.7 Causes of a poor response to erythropoiesis-stimulating agent (ESA) therapy. ACE, angiotensin-converting enzyme; EPO, erythropoietin; PRCA, pure red-cell aplasia.

Markers of iron status in CKD patients

Test	Minimum/ Maximum Value	Recommended Range
Serum ferritin	>100 µg/l <800 µg/l	200–500 µg/l
Transferrin saturation	> 20%	20%–40%
Hypochromic red cells	<10%	<6%
Reticulocyte hemoglobin content (CHr)	>29 pg/cell	29 pg/cell
Serum transferrin receptor	Not established	Not established
Erythrocyte zinc protoporphyrin	Not established	Not established

Figure 72.8 Markers of iron status and the recommended target ranges in chronic kidney disease (CKD).

Erythropoietin

- **Erythropoietin (normal range: 8- 18 mU/ml), sialoglicoprotein, 34.000 D**
- **In the interstitial cells of the renal cortex**
- **10-15 % may be produced by hepatocytes and possibly by macrophages**
- **In extra renal anemia may increase 100-1000 fold**
- **Bone marrow: hypoplastic for erythroid line without interference with leucopoiesis or megacariocytopoiesis**
- **Decreased cell life span ? (RBC from uremic to normal subject have a normal RBC survival**

Reduced oxygen carrying capacity:
organ hypoxia – aggravation of uremic symptoms

rhEPO

first generation erythropoietin agents

- 165 aa, glycosylated moiety is different
- T ½: 4 – 13 hrs after iv administration
- T ½: 24 hrs after sc administration
- Epoetin alfa (produced by genomic DNA) – 39 % oligosaccharide moiety
- Epoetin beta (produced by complementary DNA) – 24% oligosaccharide moiety
- They do not differ in pharmacokinetics and efficacy
- Dose 50 – 300 IU/kg three times per week

ARANESP
- second generation erythropoietin agent

- **Darbapoetin alfa (ARANESP) contains five N-linked carbohydrate chains, two more that rHEpo (greater stability)**
- **Increased molecular weight, greater negative charge**
- **Three-fold longer serum half-life than rhEpo (25.3 vs 8.5 hrs) when administered iv**
- **Subcutaneously administration - T ½ 48.8 hrs**
- **May be administered once a week**
- **To change from rhEpo to ARANESP we should divide the dose of rhEpo by a factor of 200**

Third generation erythropoietin agents

- **CERRA (Continuous Erythropoietin Receptor Activator) with large polimer chain - methoxy polyethylene glycol-epoetin beta): half life greater than darbopoietin - once a month (Mircera)**

- **Peginesatide (hematide): pegylated synthetic peptide that stimulate erythropoiesis (in III phase in healthy volunteeres: given once a month)**

For each 1.0g/dl decrease in blood hemoglobin level below normal, mortality rate rises 18%

Secondary effects of anemia correction on the cardiovascular system
Reduction in high cardiac output
Reduced stroke volume
Reduced heart rate
Increase in peripheral vascular resistance
Reduction in anginal episodes
Reduction in myocardial ischemia
Regression of left ventricular hypertrophy
Stabilization of left ventricular dilation
Increase in whole blood viscosity

Figure 72.4 Secondary effects of anemia correction on the cardiovascular system.

Other secondary effects of anemia correction
Reduced blood transfusions
Increased quality of life
Increased exercise capacity
Improved cognitive function
Improved sleep patterns
Improved immune function
Improved muscle function
Improved depression
Improved nutrition
Improved platelet function
(Hypertension)
(Vascular access thrombosis)

Figure 72.5 Other secondary effects of anemia correction.
Parentheses indicate negative and adverse effects.

Guidelines for Treatment with RHuEpo in Patients with CRF

Initiation:

Hgb level <11 g/dl (Hct 33%) in premenopausal women

Hgb level < 12 g/dl (Hct 36%) in adult men and postmenopausal women

NOT recommended in patients with Hgb levels > 13 g/dL

Uncontrolled hypertension: contraindication to the initiation of rHuEpo therapy

Hgb, Hct level should be measured every each week during induction therapy, and every 2 wk thereafter. Serum iron, TIBC, serum ferritin should be measured monthly for 3 months and every 2 - 3 months thereafter

Cardiovascular Disease in CKD

Many risk factors are common to both progression of kidney disease and cardiovascular complications, such as diabetes, hypertension, dyslipidemia

CKD is an independent risk factor for cardiovascular disease and all cause mortality

Rates of both stroke and myocardial infarction are higher in patients with CKD before development of ESRD

CKD is an independent risk factor for coronary heart disease

Mortality rate in patients with CKD is 10- 30 – fold higher than in normal, age-matched populations

Prevalence of left ventricular hypertrophy and congestive heart failure is strikingly elevated in patients with CKD stages 2 through 5

Cardiopulmonary Complications

- **LV hypertrophy 40%, coronary artery disease, systolic LV dysfunction, diastolic LV dysfunction (myocardial interstitial fibrosis), congestive heart failure (10%) are much more common than in matched patients without renal disease**

- **pleural effusion, cardiac tamponade (50% of patients in uremic state) – heparin must be used with caution**

- **Arrhythmias often associated with hyperkalemia**

Cardiovascular disease is the most important cause of death in patients with ESRD

Hypertension

- **May complicate chronic parenchymal renal disease even before azotemia develops**
- **ESRD: it occurs in 80-90% of patients**
- **Essential hypertension may cause nephrosclerosis and progressive renal failure**
- **Hypertension accelerate loss of nephrons (high intraglomerular pressure, nephrosclerosis)**
- **Elevated rennin production**
- **Sodium chloride retention (even if overt edema is not present)**
- **Failure to produce some vasodilatators (e.g. prostaglandins)**
- **Inhibition of nitric oxide synthase (↓NO) by accumulation of dimethylarginine in renal failure**
- **Enhanced peripheral sympathetic activity**

Hypertension

Uncontrolled hypertension accelerates the rate of progression regardless of the cause of renal failure

Clinical trials and epidemiologic studies indicate that hypertension is a major risk factor for progressive kidney disease

Adequate blood pressure control is achieved in only 11% of patients with CKD

The goal blood pressure for patients with CKD is <130/80 mmHg, but with cautious < systolic < 110 mmHg (diabetes with CKD <120/75 mmHg)

Treatment of hypertension

- **Salt restriction (sodium intake < 100 mEq/day; optimal < 70 (4.0g/day)**
- **Loop diuretic: furosemide (thiazides lose their effectiveness as GFR falls below 40 ml/min)**
- **ACEi, ARB (combination - greater antiproteinuric effect)**
- **Elevation in serum creatinine level of 30 - 35% above baseline - no reason for discontinuation - control creatinine and potassium level within 3 - 5 days after introduction**
- **calcium blockers (non - dihydropyridine preffered - antiproteinuric effect), α-blockers, vasodilatators**
- **During dialysis therapy in the most patients blood pressure can be regulated by control of plasma volume with ultrafiltration and modest dietary salt restriction**
- **In the past bilateral nephrectomy was sometimes required; now treatment with ACEi, calcium channel blockers is effective**
- **If hypertension is not controlled by dialysis, hypotensive drugs should be used before dialysis with a caution, especially in patients with autonomic nerve insufficiency – hypotension during dialysis (drugs after HD or on the day between HD)**
- **Transplantation: in about 50%- 80% of patients (CsA, GS, tacrolimus)**

Disorders of Lipid Metabolism

- **Risk factor of onset and progression of CKD , cardiovascular disease**
- **↓ activity of lipoprotein lipase**
- **↑ hepatic synthesis of VLDLs**
- **Uremic patients - plasma cholesterol level is usually normal (↓ HDL, ↑ LDL), ↑Lp(a)**
- **Markers of inflammation and oxidative stress: ↑ CRP, ↑IL-6, ↑ TNf-a - used for experimental purpose**

Treatment: LDL-Ch <100 mg/dL;statins - beneficial effects of statins on stiffening and endothelia function

Homocysteine

Studies in CKD and non-CKD populations indicate that hyperhomocysteinemia is a risk factor for cardiovascular death

Plasma homocysteine concentration rises with decreasing renal function in CKD.

The mechanism of hyperhomocysteinemia in CKD is incompletely understood, however, abnormal enzyme activity, substrate limitation, and abnormal renal excretion have all been cited as possible causes

Hyperhomocysteinemia is associated with progression of CKD in diabetic and non-diabetic patients

Treatment: administration of folic acid 5 mg per day in patients with CKD can lower plasma homocysteine level (however is not routinely recommended, because whether long-term lowering of homocysteine reduces the risk of either cardiovascular disease or progression to CKD is not known)

Coagulation abnormalities

- **A bleeding tendency manifested by epistaxis, menorrhagia, gastrointestinal tract bleeding, prominent bruising after trauma is common in advanced CKD**
- **Defect in a qualitative defect in platelet function**
- **Abnormal factor VIII function**
- **decreased protein C and S activity**
- **A prolonged bleeding time although the partial thromboplastin time, prothrombin time, clotting time are all within normal limits**
- **The factors in uremic serum that induce qualitative platelets function are not well delineated, but dialysis corrects the defect**
- **Plasma fibrinolytic activity is decreased but improves after dialysis**

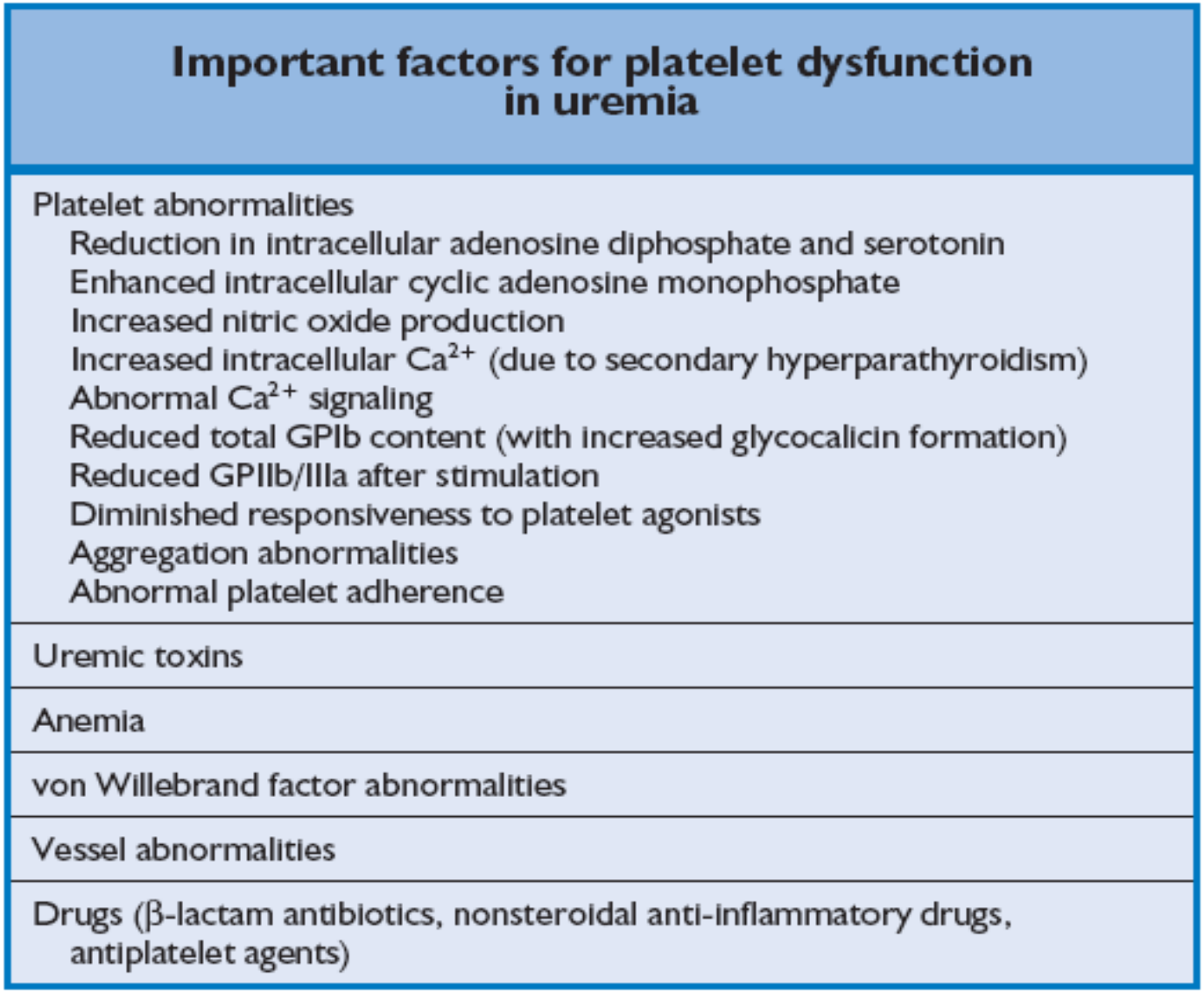


Figure 73.3 Important factors for platelet dysfunction in uremia.

Therapeutic approaches to correct uremic bleeding tendency, ranked in order of clinical usage

Measure	Comments
Correct anemia	Increase hemoglobin to > 10 g/dl with rHuEpo or darbepoietin alfa. Use packed red blood cells in emergencies (with monitoring of serum potassium).
Adequate dialysis	Increase Kt/V > 1.2 in hemodialysis and Kt/V > 1.7 in peritoneal dialysis patients.
Avoid or monitor heparin usage	Note persistent anticoagulation after hemodialysis; monitor anti-Xa levels if LMWH is used at a GFR < 30 ml/min; in high-risk patients on hemodialysis, reduce, eliminate, or replace heparin with citrate; administer protamine sulfate, 1 mg per 100 U of heparin infused over 10 min, in emergencies to antagonize heparin.
Withdraw antiplatelet agents	Stop dipyridamole or clopidogrel at least 72 hours before surgery; stop acetylsalicylic acid 7–10 days before surgery.
Administer DDAVP	One hour before surgery, administer DDAVP intravenously (0.3–0.4 μg/kg in 50 ml normal saline over 20–30 min), subcutaneously (0.3 μg/kg), or intranasally (2–3 μg/kg).
Administer cryoprecipitate	One hour before surgery, administer cryoprecipitate (infusion of about 10 units).
Administer estrogens	Administer conjugated estrogen, 0.6 mg/kg per day intravenously or 25–50 mg/kg per day orally, or estradiol, 50–100 μg twice weekly transdermally.

Figure 73.4 Therapeutic approaches to correct uremic bleeding tendency, ranked in order of clinical use. DDAVP, desmopressin acetate; GFR, glomerular filtration rate; LMWH, low-molecular-weight heparin; rHuEPO, recombinant human erythropoietin.

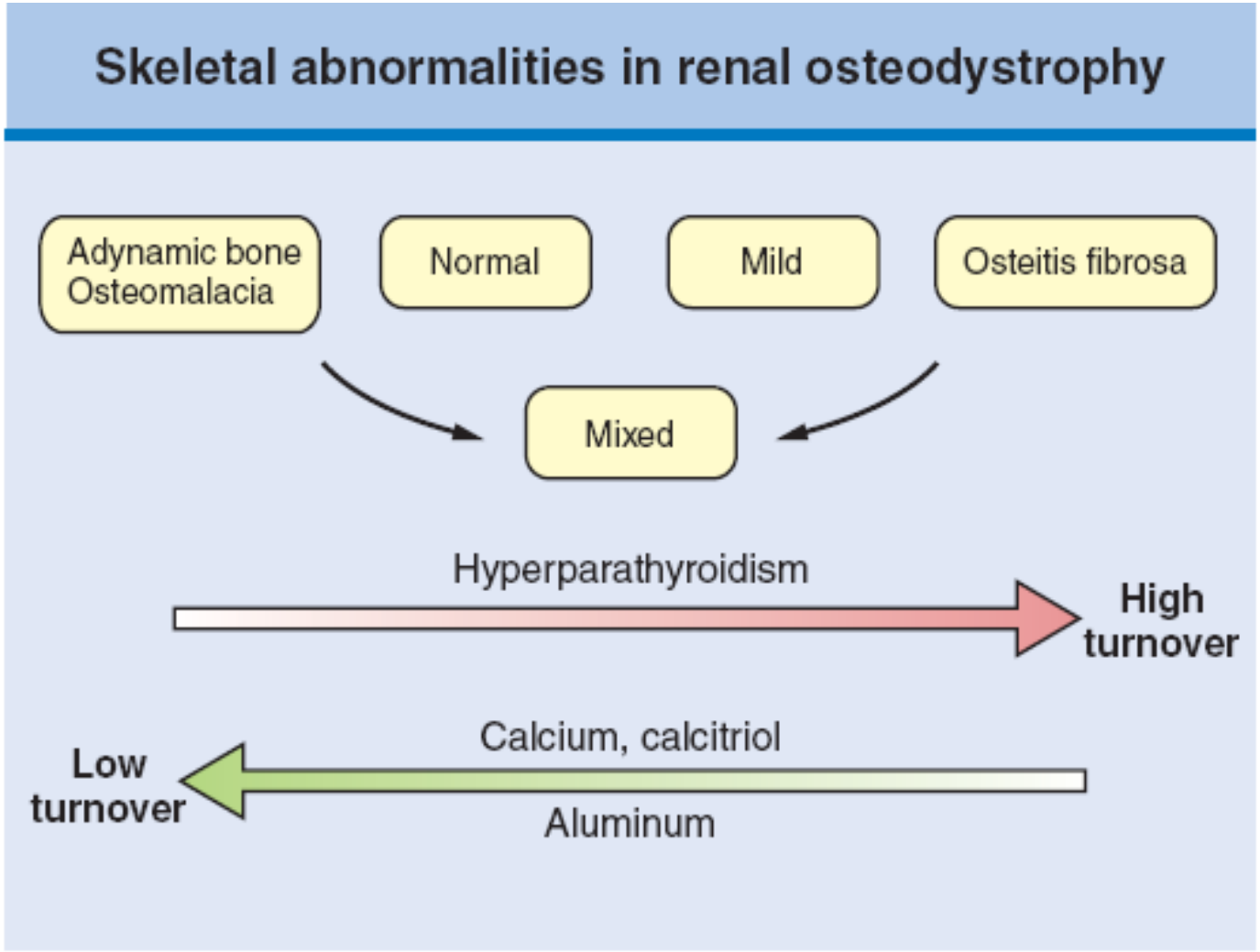


Figure 74.1 The spectrum of renal osteodystrophy. The range of skeletal abnormalities in renal bone disease encompasses syndromes with both high and low bone turnover.

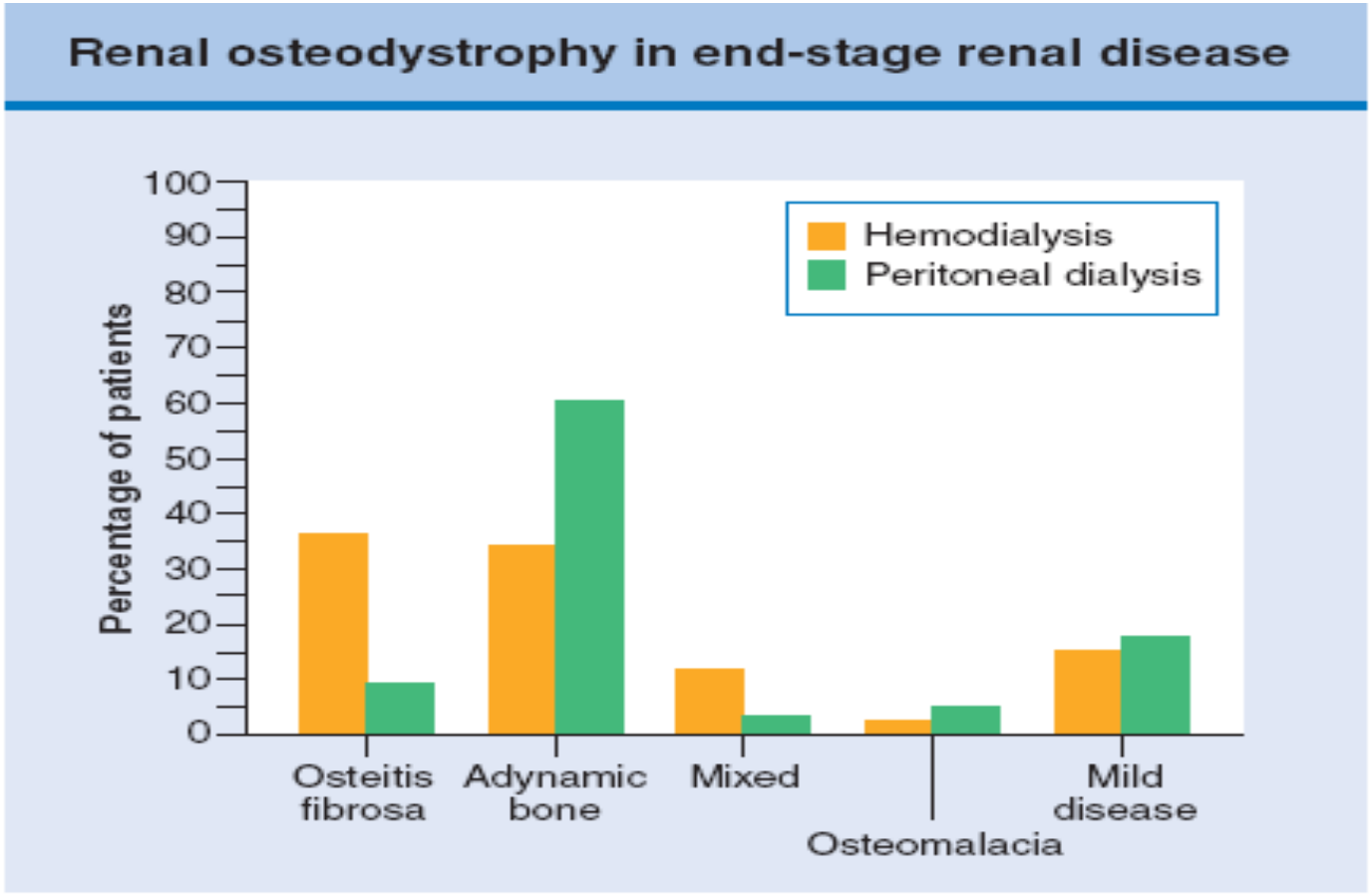


Figure 74.2 Prevalence of renal osteodystrophy in patients with end-stage renal disease. The pattern of renal osteodystrophy varied with the dialysis modality in a group of patients on hemodialysis (n = 117) or peritoneal dialysis (n = 142).

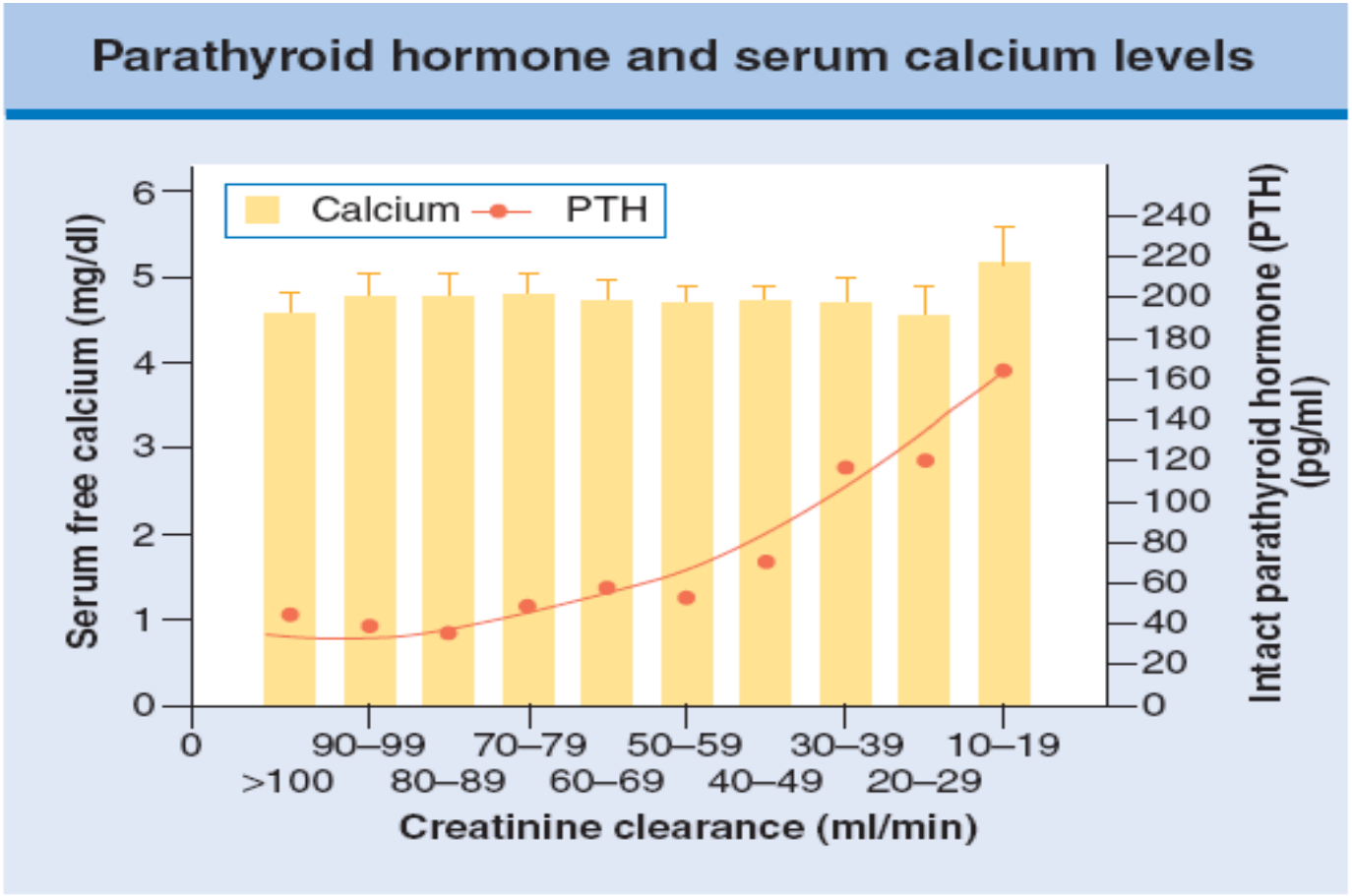


Figure 74.3 Ionized calcium and parathyroid hormone (PTH) levels in chronic renal failure. Levels of ionized calcium are maintained in advancing renal failure by progressive increases in PTH.

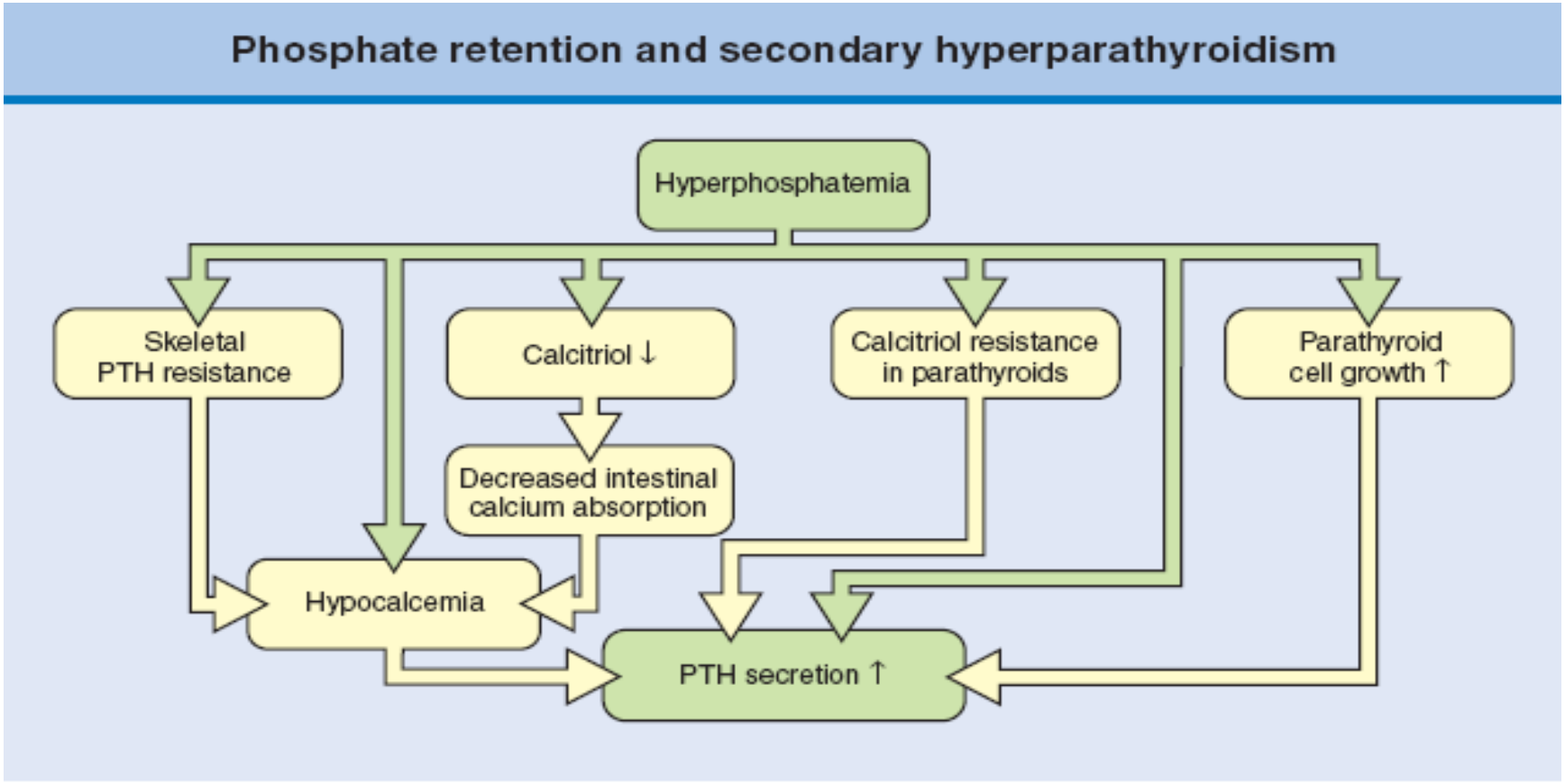


Figure 74.4 Role of phosphate retention in the pathogenesis of secondary hyperparathyroidism. Hyperphosphatemia stimulates parathyroid hormone (PTH) secretion indirectly by inducing hypocalcemia, skeletal resistance to PTH, low levels of calcitriol, and calcitriol resistance. Hyperphosphatemia also has direct effects on the parathyroid gland to increase PTH secretion and parathyroid cell growth.

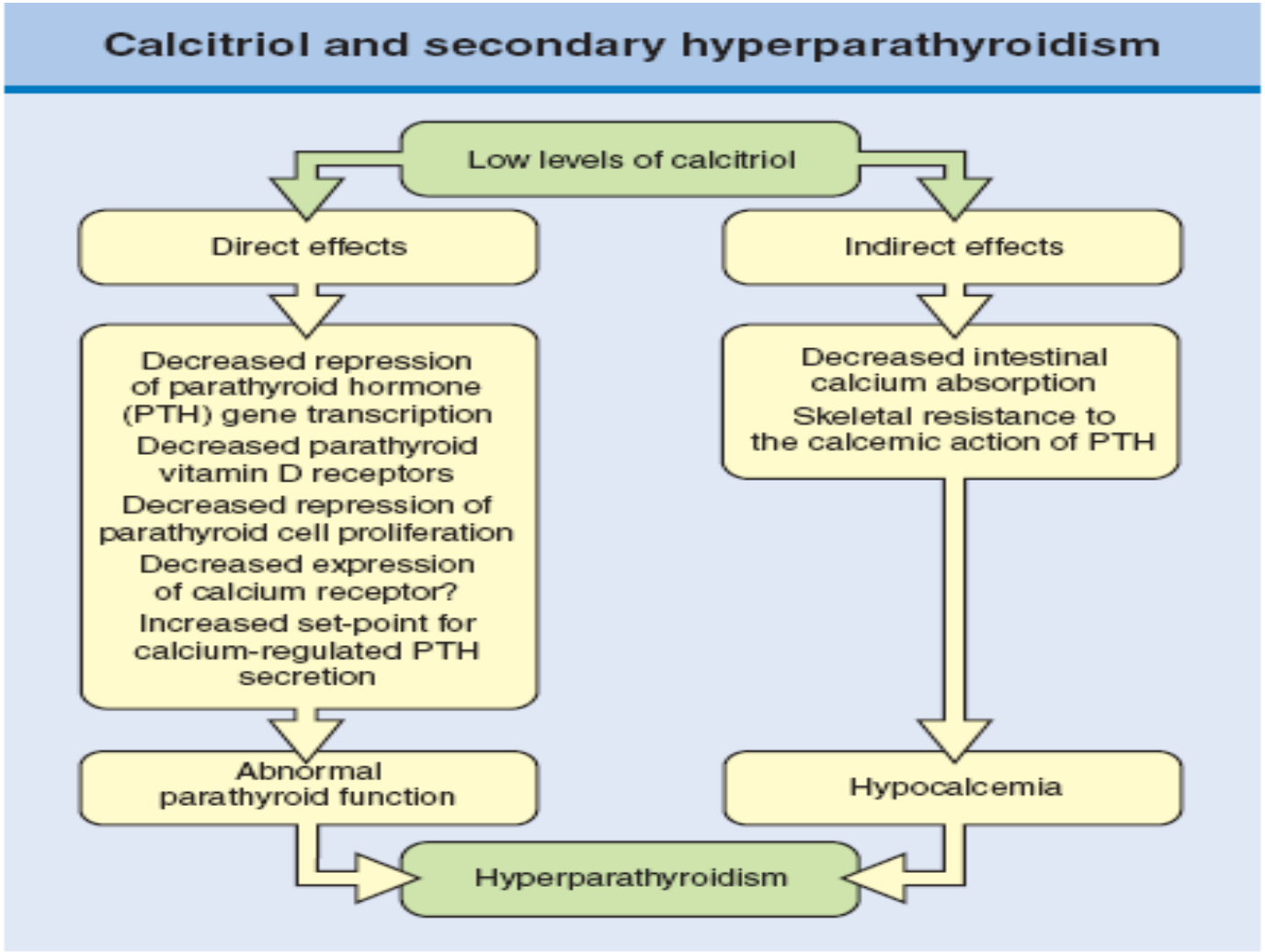


Figure 74.5 Role of low levels of calcitriol in the pathogenesis of secondary hyperparathyroidism.

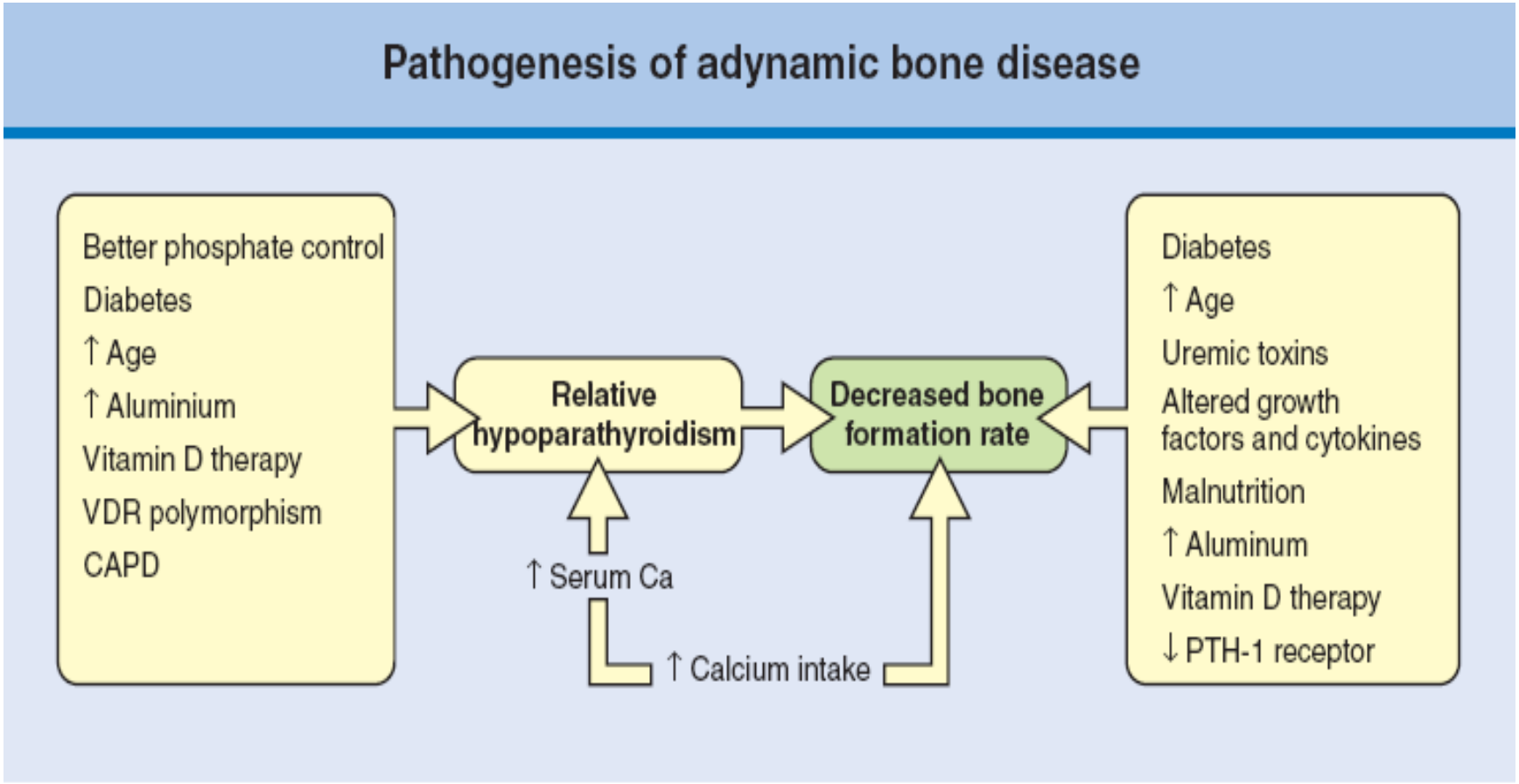


Figure 74.7 Pathogenesis of adynamic bone disease. CAPD, continuous ambulatory peritoneal dialysis; PTH, parathyroid hormone; VDR, vitamn D receptor.

(Adapted from Couttenye MM, D'Haese PC, Verschoren WJ, et al: Low bone turnover in patients with renal failure. Kidney Int 1999; 56:S70–S76.)

Renal Osteodystrophy

- **In the children retardation of growth**
- **In the adult – bone pain, fractures, collapse of vertebre, necrosis of femoral heads, skeletal deformities**
- **Calciphylaxis:**

  metastatic calcification

  medial calcifilation of arteries, with ischemic necrosis

  calcification of soft tissue and skin periarthritis

  conjuncival calcification

Renal Osteodystrophy

- **↑ bone associated-proteins: osteocalcin, bone morphogenetic protein 2a (BMP2a), alkaline phosphatase, osteonectin**
- **↓p21 , a cykline-dependent kinase complex**
- **bone biopsy – the most accurate assessment**

Goal of treatment

- **P04 2.7 - 4.6 mg/dL (3 - 4 stage), 3.5 - 5.5 mg/dL (stage 5)**
- **CaxPO4 product < 55 mg2/kg2 in patients with stage 3 - 5 disease (higher: increased risk of calcification of soft tissue, vessels)**
- **Ca 8.4 mg/dL - 9.5 mg/dL**
- **iPTH 35 - 70 pg/mL (GFR 30 - 59 ml/min); 70 - 110 pg/mL (GFR 15 - 29 ml/min), 150 - 300 pg/mL (stage 5)**
- **1 - 84 PTH (bioPTH - second genaration test): 50 - 60% of those achieved with intact assay**
- **Monitoring of PTH level (because of skeletal resistance to PTH levels of three times normal may be best)**

Treatment

- **Diete: restriction dietary phosphate to 800 - 1000 mg/day (protein restriction: diary products, beans, colas, fish)**
- **Correction of acidosis above 22 mEq/L(orally Na_2C0_3: 0.5 - 1 mEq/kg/day, or citrate - without bloating produced by bicarbonates)**
- **Calcium based phosphate binders (calcium carbonate, calcium acetate: total elemental calcium intake from binders <1500 mg/day, total from diete and binders 2000 mg/day) - risk of hypercalcemia, calcification**
- **Cationic polymer binding phosphate through ion exchange - sevelamer (Renagel) - no risk of hypercalcemia**
- **Lanthanum carboanate (Fosrenol)**
- **vit D3, analogs (paricalcitol, doxercalciferol, alphadiol, calcitriol, alphacalcidol, falecalcitriol, 22-oxycalcitriol (shoud not be given at stage 3, 4 unless serum phosphate< 4.6 mg/dL, at stage 5 < 5.5 mg/dL) - prescription of calcitriol with careful follow-up serum calcium and phosphorus levels**
- **Calcimimetics: cinacalcet - increases the sensivity of CaSR**
- **Dialysate calcium level may be lowered**
- **Subtotal parathyreoidectomy**
- **Kidney transplantation**

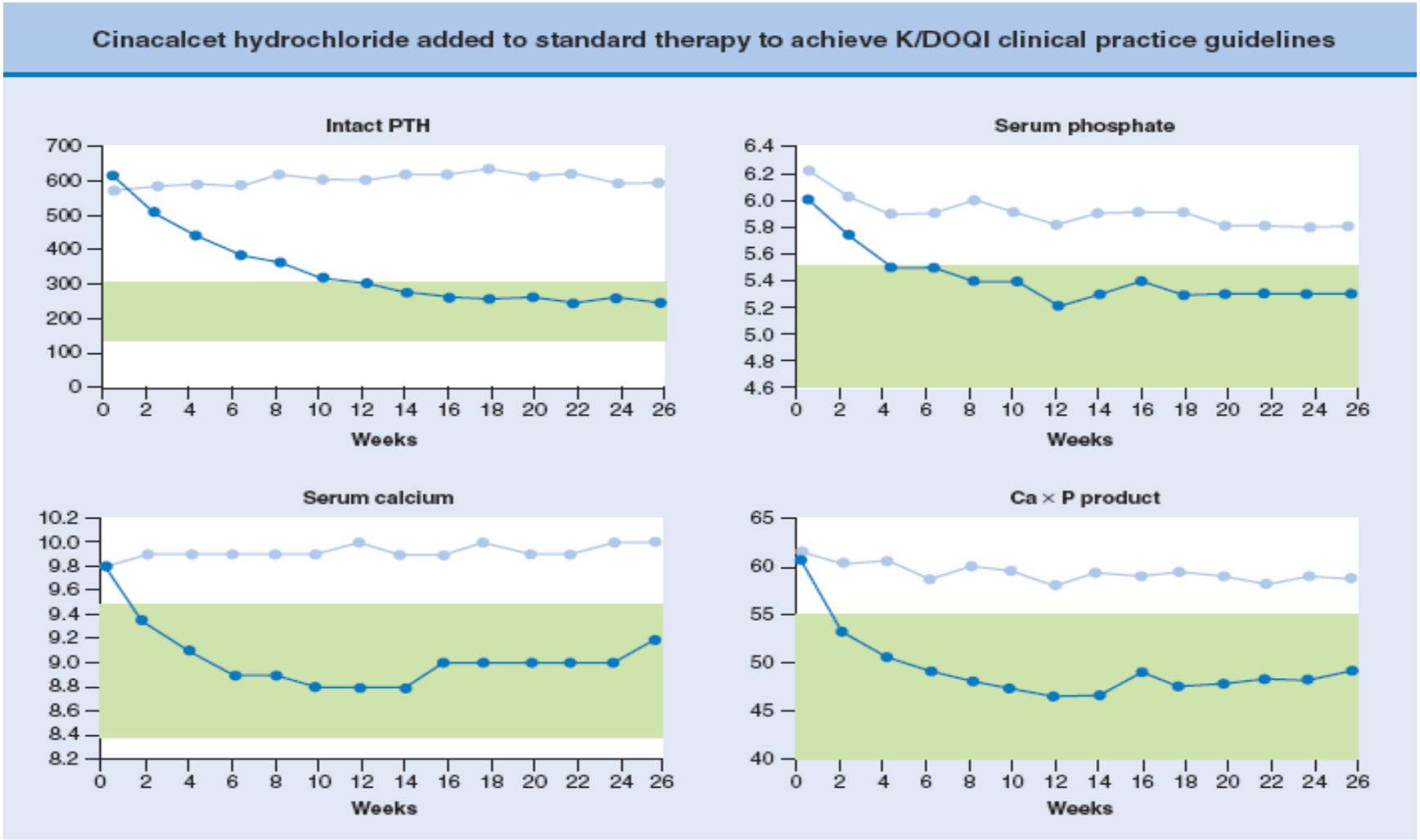


Figure 74.13 Cinacalcet hydrochloride (*dark blue line*) added to standard therapy (*light blue line*) facilitates the achievement of the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines. K/DOQI target ranges are indicated by the *shaded green* areas. PTH, parathyroid hormone.

(Adapted from Moe SM, Chertow GM, Coburn JW, et al: Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCl. Kidney Int 2005;67:760–771.)

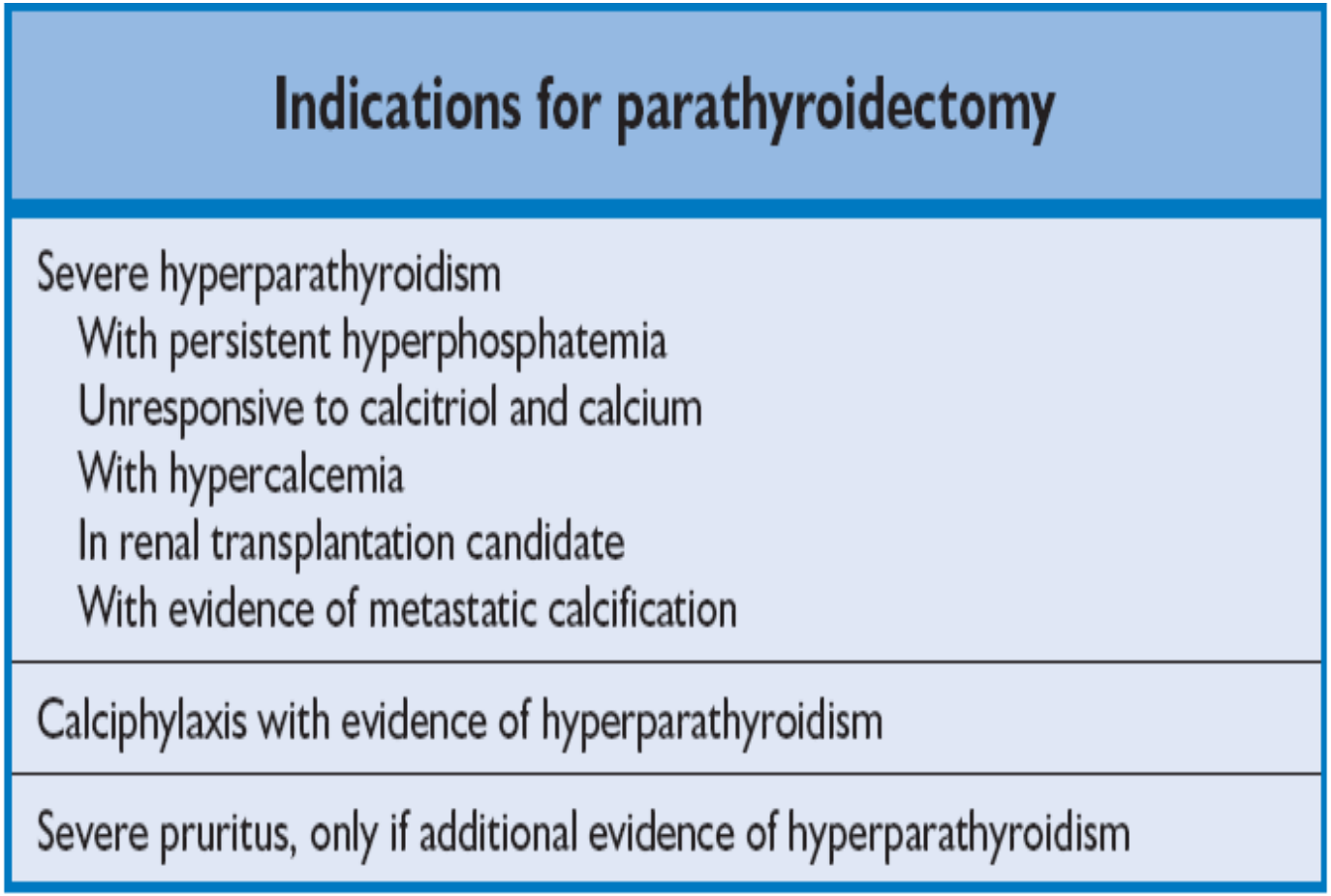


Figure 74.14 Indications for parathyroidectomy.

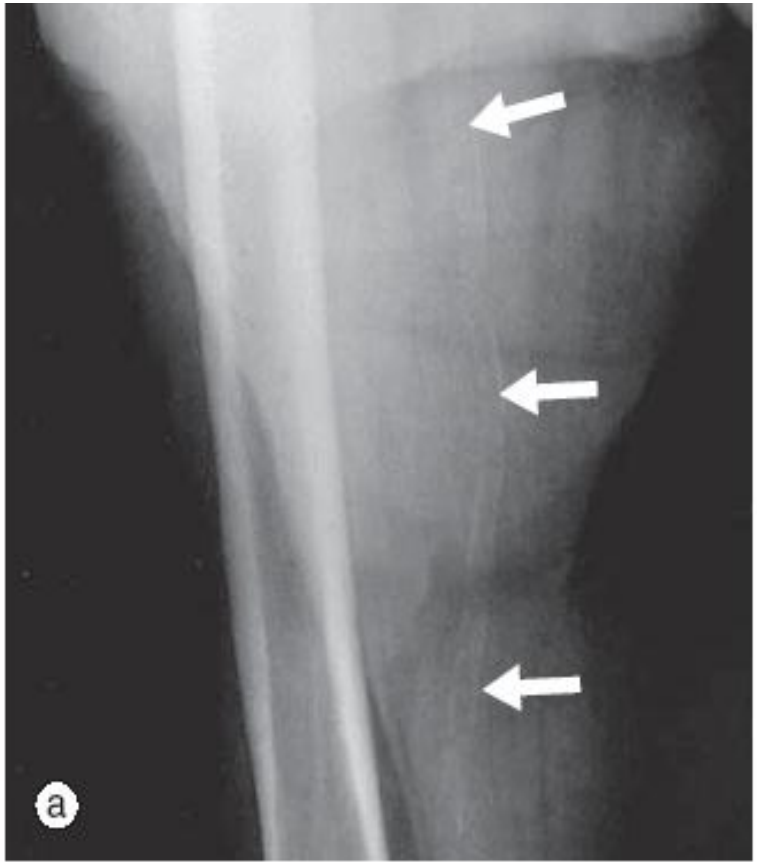


Figure 74.9A Extraskeletal calcification in chronic renal failure.
a, Arterial calcification (*arrows*). *b,* Pulmonary calcification. *c,* Periarticular calcification (*arrows*).

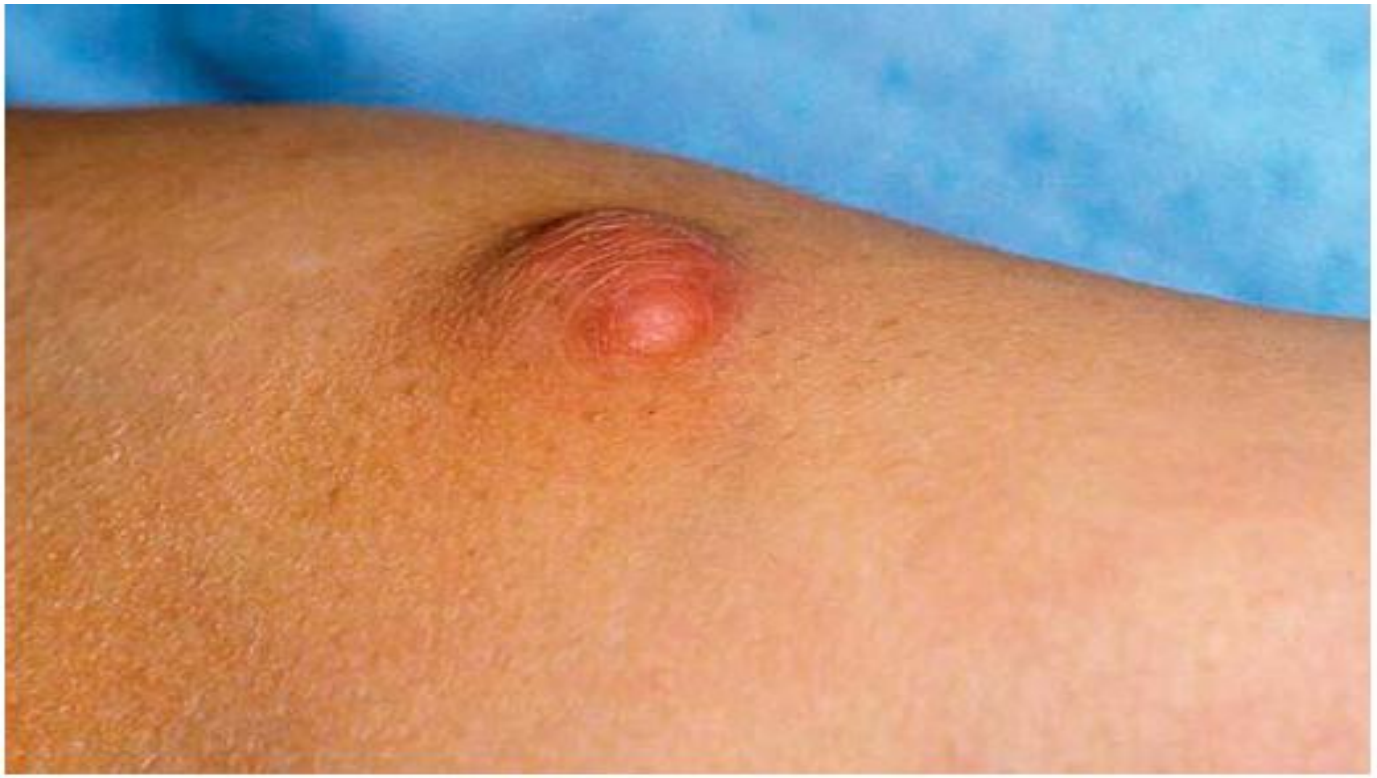


Figure 78.5 Benign nodular calcification (calcinosis cutis).
Firm subcutaneous nodule adjacent to the elbow.

Radiologic diagnostic criteria for $A\beta_2M$-amyloidosis–associated cystic bone lesions
Diameter of lesions >5 mm in wrists and >10 mm in shoulders and hips
Normal joint space adjacent to the bone defect
Exclusion of small subchondral cysts located in the immediate weight-bearing area of the joint
Exclusion of defects of the synovial inclusion type
Increase of defect diameter >30% per year
Presence of defects in at least two joints

Figure 75.5 Radiologic diagnostic criteria for $A\beta_2M$-amyloidosis– associated cystic bone lesions.

(From van Ypersele de Strihou C, Jadoul M, et al: Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int 1991;39: 1012–1019.)

Recommendations for the prevention and management of $A\beta_2M$-amyloidosis

Recommendations for Prevention
Ignore the issue of $A\beta_2M$-amyloidosis in all patients whose life expectancy on dialysis is <5 years (i.e., the time when clinical manifestations first appear).
In all other patients, attempt renal transplantation whenever possible.
On hemodialysis, use bicarbonate-buffered dialysate and minimize microbiologic dialysate contamination.
Use high-flux hemodialysis or hemodiafiltration in those at high risk for $A\beta_2M$-amyloidosis (i.e., the elderly and all patients, independent of age, who have little chance of receiving a renal transplant).
Recommendations for Treatment of Symptomatic $A\beta_2M$-Amyloidosis
Initiate symptomatic, usually orthopedic, measures depending on musculoskeletal site and symptoms of amyloid deposits.
Attempt renal transplantation as soon as possible.
If renal transplantation is not a short-term option, consider change to hemodialysis, or preferably hemodiafiltration, using high-flux synthetic membranes and microbiologically clean dialysate (addition of adsorbent columns may also be considered, although their efficacy is less well established) to at least retard further progress.
If severe, disabling symptoms persist despite the above measures, initiate prednisone therapy at 0.1 mg/kg body weight per day.

Figure 75.6 Recommendations for the prevention and management of $A\beta_2M$-amyloidosis.

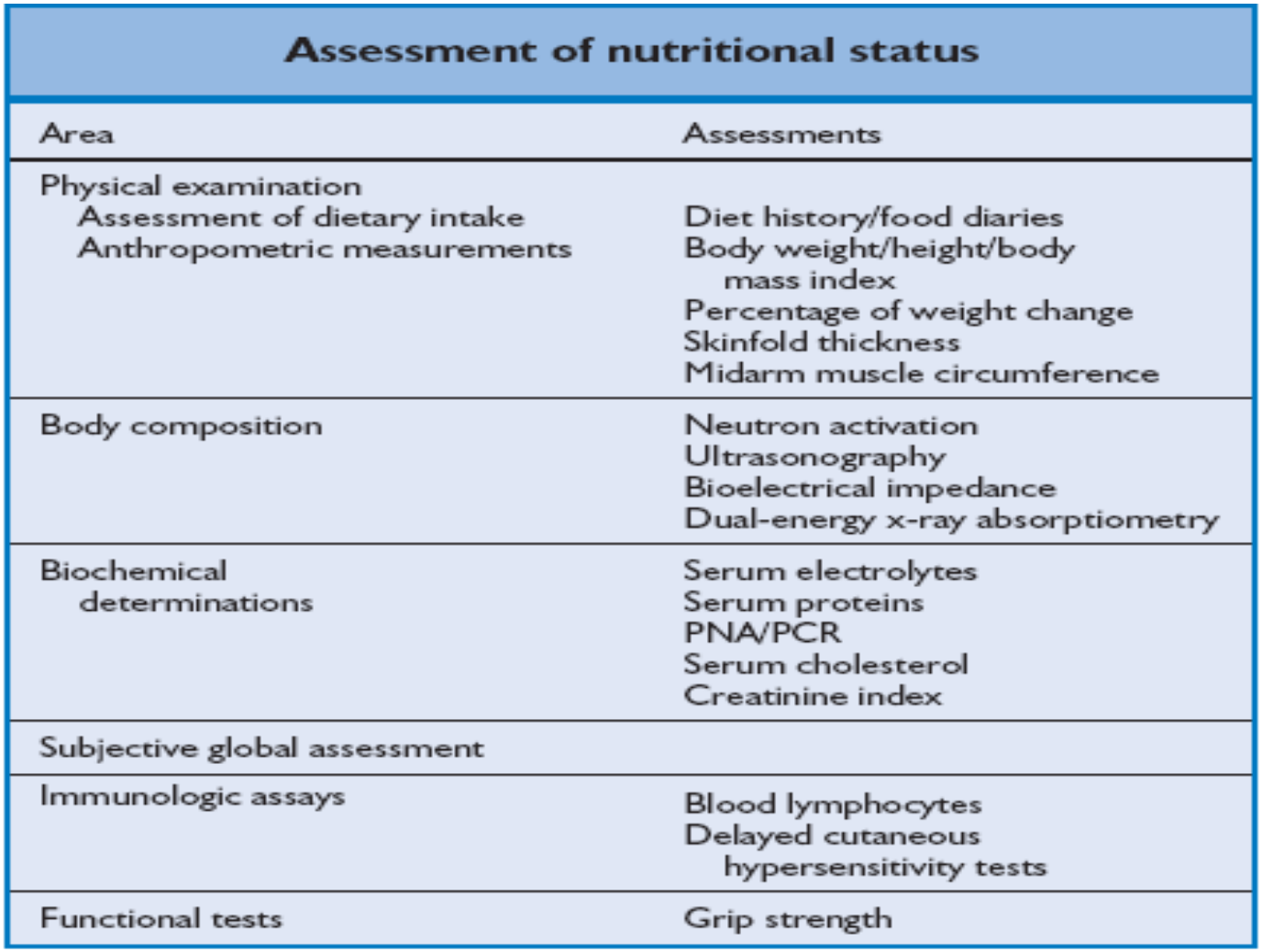
Malnutrition

- **Negative nitrogen balance:**

- **Anorexia (common with 4 stage CKD):**

  weight loss, muscle atrophy, weakness, dryness of skin

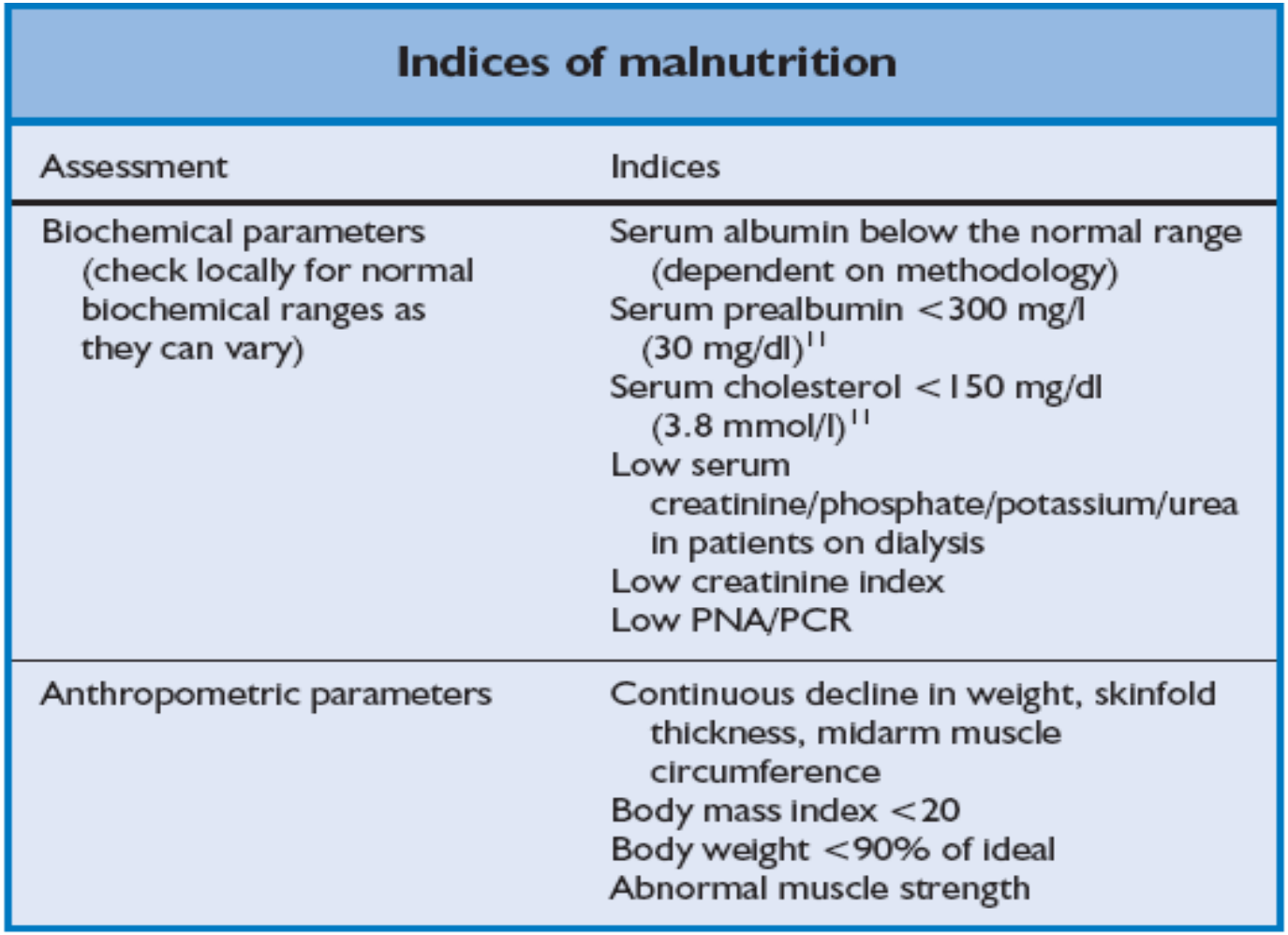
- **Morbidity and mortality rate are increased**



Assessment of nutritional status	
Area	Assessments
Physical examination Assessment of dietary intake Anthropometric measurements	 Diet history/food diaries Body weight/height/body mass index Percentage of weight change Skinfold thickness Midarm muscle circumference
Body composition	Neutron activation Ultrasonography Bioelectrical impedance Dual-energy x-ray absorptiometry
Biochemical determinations	Serum electrolytes Serum proteins PNA/PCR Serum cholesterol Creatinine index
Subjective global assessment	
Immunologic assays	Blood lymphocytes Delayed cutaneous hypersensitivity tests
Functional tests	Grip strength

Figure 77.7 Assessment of nutritional status. Common methods used to assess nutritional status are shown. PNA, protein equivalent of total nitrogen appearance; PCR, protein catabolic rate.

Figure 77.8 Routine measurement of skinfold thickness. The dominant arm that does not have the fistula and graft is used in patients with renal failure.



Indices of malnutrition

Assessment	Indices
Biochemical parameters (check locally for normal biochemical ranges as they can vary)	Serum albumin below the normal range (dependent on methodology) Serum prealbumin <300 mg/l (30 mg/dl)[11] Serum cholesterol <150 mg/dl (3.8 mmol/l)[11] Low serum creatinine/phosphate/potassium/urea in patients on dialysis Low creatinine index Low PNA/PCR
Anthropometric parameters	Continuous decline in weight, skinfold thickness, midarm muscle circumference Body mass index <20 Body weight <90% of ideal Abnormal muscle strength

Figure 77.12 Indices of malnutrition. PNA, protein equivalent of total nitrogen appearance; PCR, protein catabolic rate.

Nutritional recommendations in chronic kidney disease

Daily Intake	Predialysis CKD	Hemodialysis	Peritoneal Dialysis
Protein (g/kg body weight) (See KDOQI[11] for estimation of adjusted edema-free body weight)	0.6–1.0 (level of restriction depends on the view of the clinician) 1.0 for nephrotic syndrome	1.2[23]	1.0–1.3[23,30]
Energy (kcal/kg body weight) (See KDOQI[11] for estimation of adjusted edema-free body weight)	35[23](<60 yr) 30–35[23](>60 yr)	35[23](<60 yr) 30–35[23](>60 yr)	35,[23,30] including dialysate calories (<60 yr) 30–35,[23,30] including dialysate calories (>60 yr)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic (>5.5 mmol/l)	Reduce if hyperkalemic (>5.5 mmol/l)	Reduce if hyperkalemic; potassium restriction is generally not required
	If hyperkalemic advice will take the form of decreasing certain fruits and vegetables, milk, and some miscellaneous foods and giving information about cooking methods		
Phosphorus	Reduce, level dependent on protein intake		
	Advice will take the form of reducing dairy products, offal, certain shellfish, and some miscellaneous foods and giving information about the timing of binders with high-phosphorus meals and snacks		
Calcium	In CKD stages 3–5 total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day

Figure 77.13 Nutritional recommendations in chronic kidney disease (CKD). Recommendations are for typical patients, but should always be individualized based on clinical, biochemical, and anthropometric indices. KDOQI, Kidney Disease Outcomes Quality Initiative.

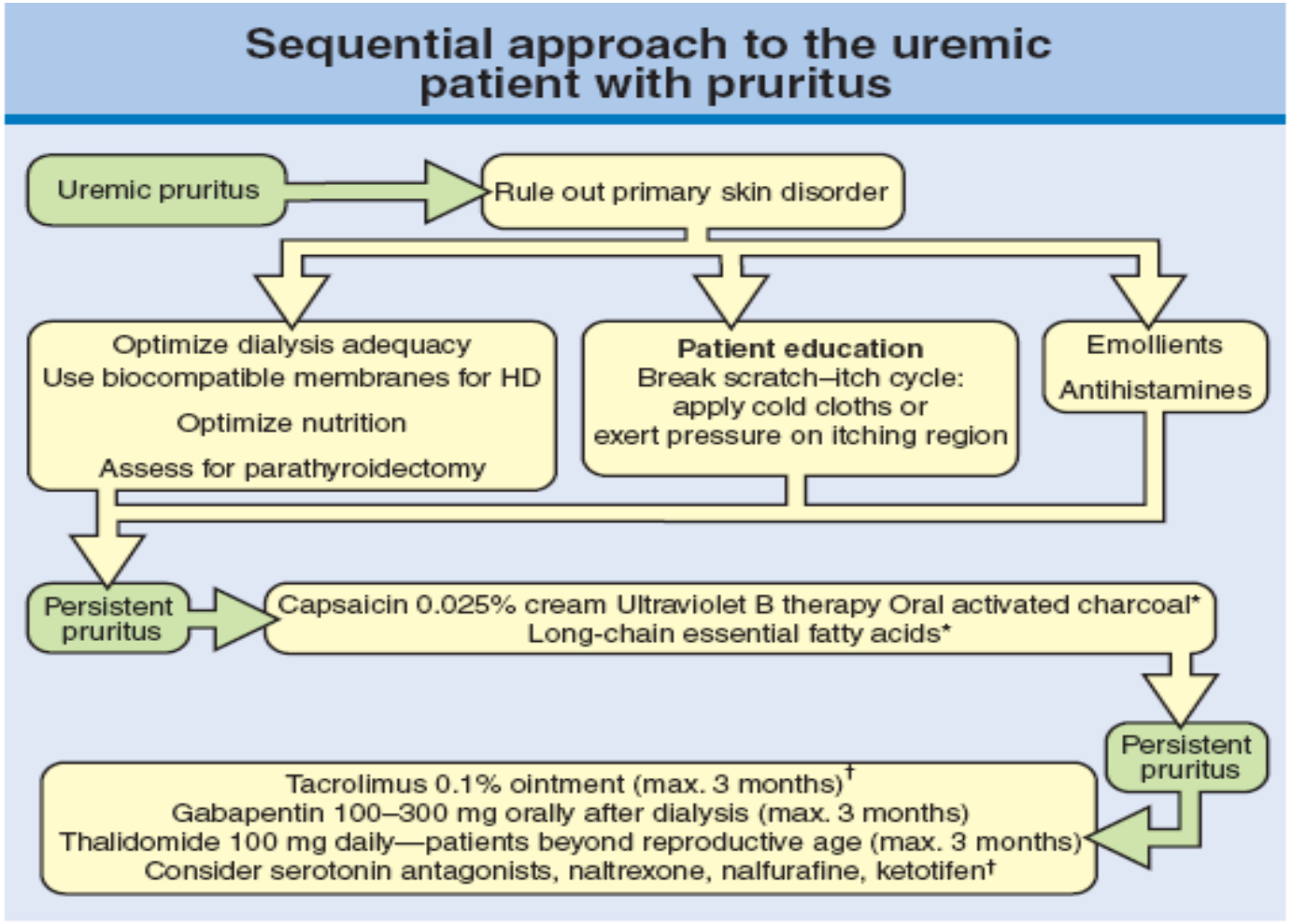


Figure 78.3 Sequential approach to the uremic patient with pruritus. *See text for details. †Therapeutic benefit in studies has been described variably; see text for details.

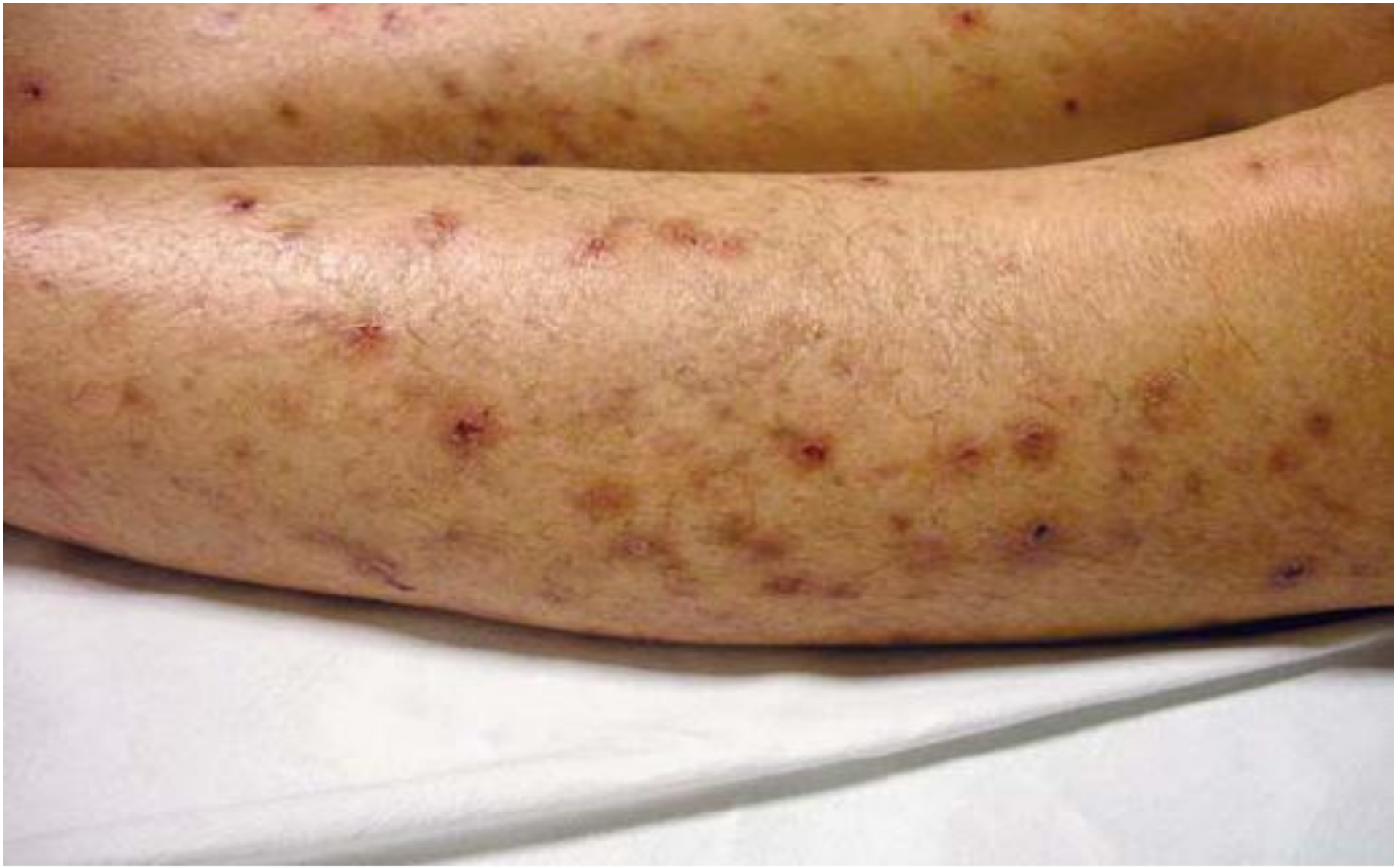


Figure 78.2 Prurigo nodularis.

(Courtesy of I. Macdougall.)

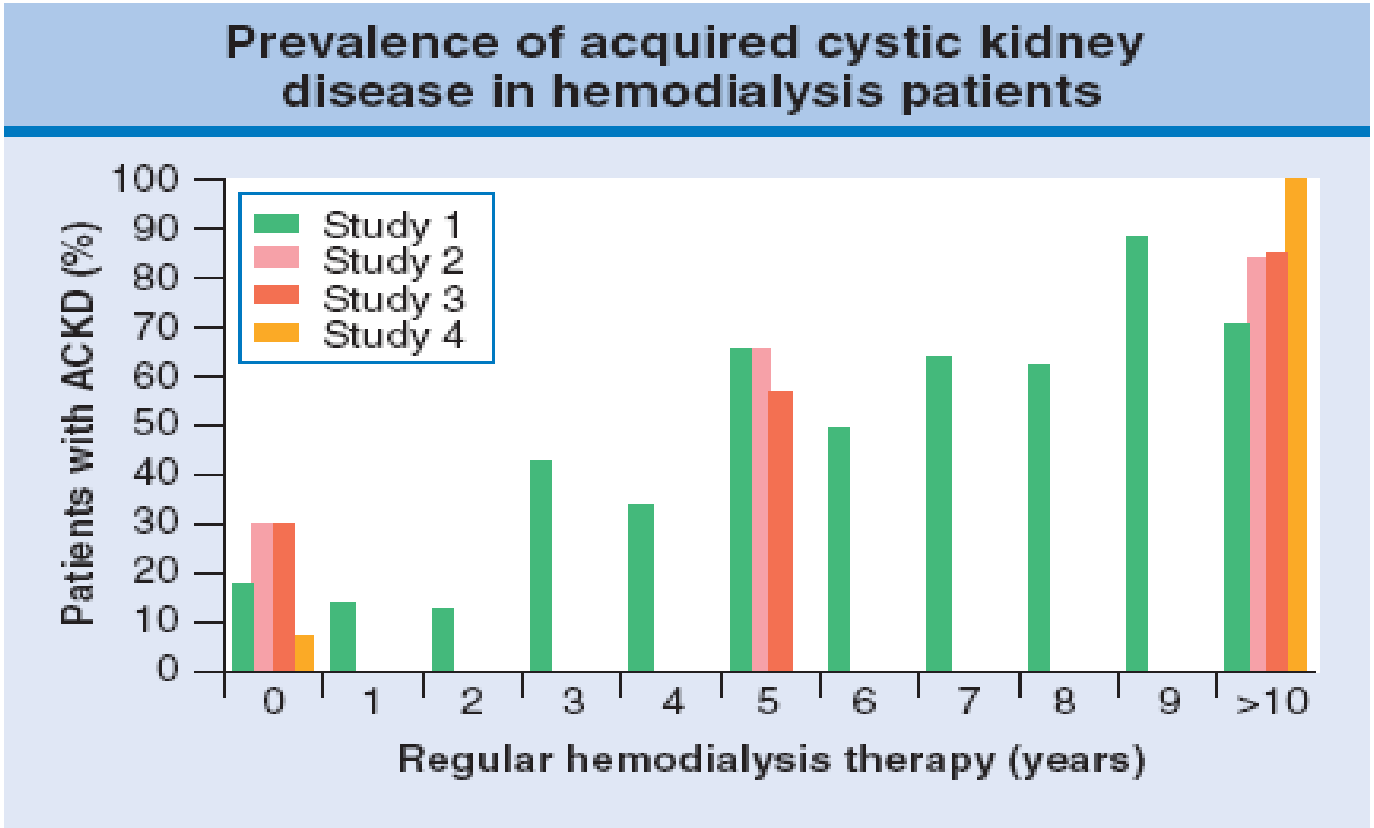


Figure 79.2 Prevalence of acquired cystic kidney disease (ACKD) in hemodialysis patients. Summary of reported ACKD prevalences in chronic hemodialysis patients in relation to the length of hemodialysis treatment. Four separate studies are shown.

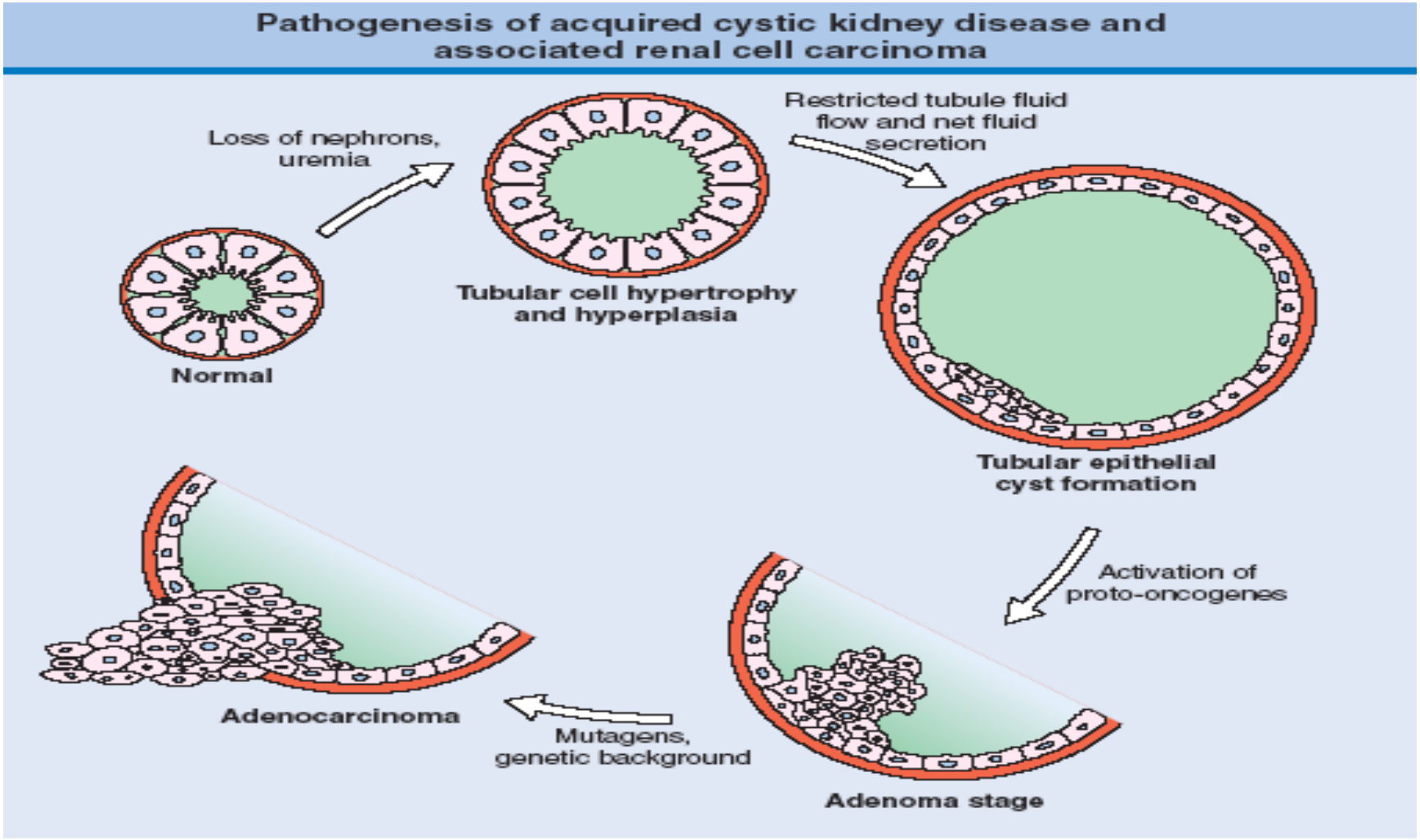


Figure 79.1 Pathogenesis of acquired cystic kidney disease (ACKD) and associated renal cell carcinoma. Diagram of events leading to the development of ACKD and subsequent malignant transformation.

(Adapted from Grantham J: Acquired cystic kidney disease. Kidney Int 1991;40:143–152.)

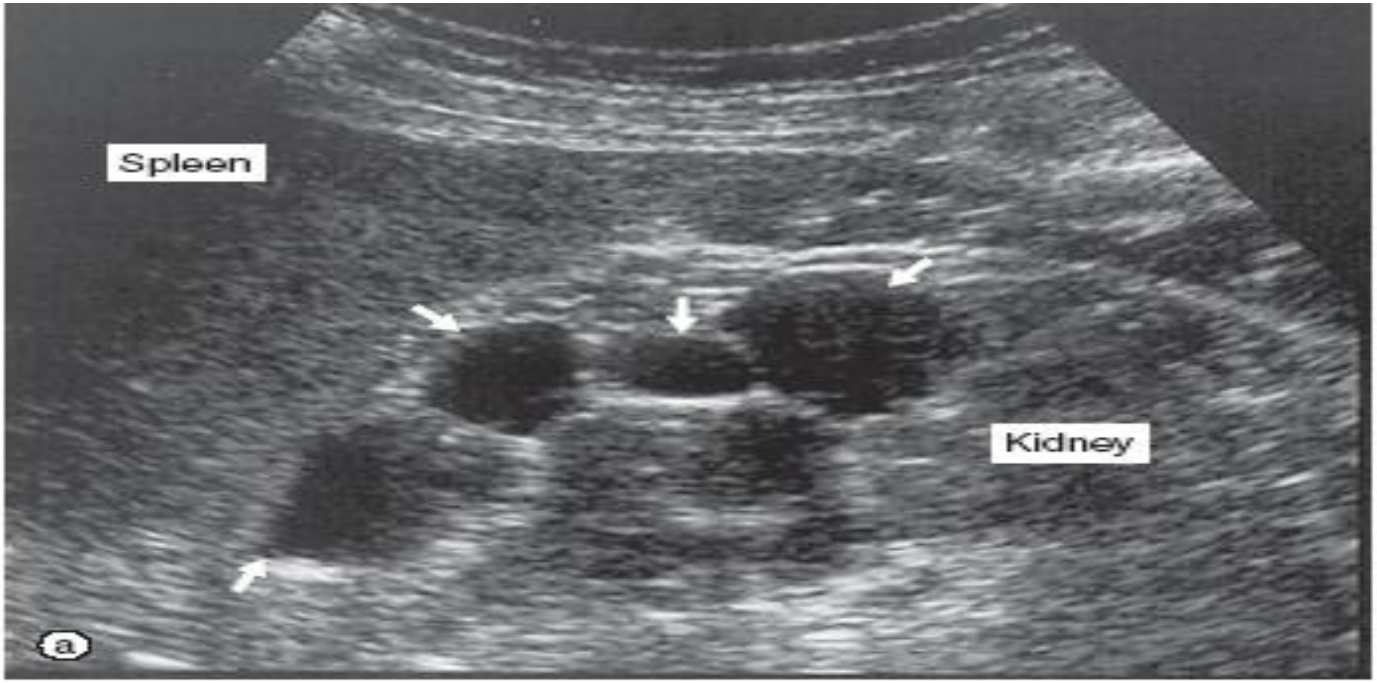


Figure 79.3A Imaging studies in acquired cystic kidney disease (ACKD). *a,* Ultrasound image of the left native kidney of a patient after 16 years of hemodialysis. Multiple cysts (*arrows*) are present in the renal cortex. *b,* Computed tomography image of a patient after 5 years of hemodialysis demonstrating multiple cysts within the right kidney (*white dashed circle*). This patient underwent a tumor nephrectomy of the left kidney 9 years prior to developing end-stage renal disease. *c,* Contrast-enhanced computed tomography image of a renal transplant recipient who developed a renal cell carcinoma originating in the left native kidney with ACKD (*white dashed circle*).

Neuromuscular abnormalities

- **Central neuropathy (uremic encephalopathy) : asterix, convulsions, psychosis, insomnia, inability to concentrate, loss of memory, confusion, hallucinations, delirium**
- **EEG – slow-wave pattern (↑ Ca in the brain, ↑ PTH)**

- **Autonomic neuropathy: impotence, absence of sweating, dialysis hypotension**

- **Peripheral neuropathy**

Prolonged nerve conduction time

Cramps of limbs muscle, intermittent numbness of the hands and feet

Restless leg syndrome: uncomfortable sensations in the legs occurring during the rest and relived by movement

NO TREATMENT

Differential diagnosis of uremic encephalopathy

Differential Diagnosis	Comment
Hypertensive encephalopathy	
Systemic inflammatory response syndrome (SIRS)	Observed in septic patients
Systemic vasculitis	Vasculitis or lupus with cerebral involvement
Drug-induced neurotoxicity	
Analgesics	Meperidine, codeine, morphine, gabapentin
Antibiotics	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy)
Psychotropics	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine
Chemotherapy	Cyclosporine, cisplatinum, ifosfamide
Others	High doses loop diuretics (ototoxic), ephedrine, methyldopa, aluminum
Cerebral atheroembolic disease	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia
Subdural hematoma	
Posterior leukoencephalopathy	Observed particularly following renal transplantation due to reversible, abnormal permeability of the blood-brain barrier Often manisfests as headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies.

Figure 76.3 Differential diagnosis of uremic encephalopathy.

Gastrointestinal Tract Disturbances

- **They appear until GFR < 10 ml/min**
- **Anorexia, nausea, vomiting (mainly in the early morning)**
- **Gastrointestinal bleeding (from the mouth the rectum)**
- **The lesions: shallow mucosal ulcerations that bleed slowly – the site of chronic blood loss**
- **In uremia gastric acid secretion is depressed in 40% of patients in 60% of patients is in normal range**
- **Plasma gastrin immunoreactivity increases progressively with renal failure (true gastrin or small peptides with gastrin like antigen – inability diseased kidney to metabolize low molecular-weight protein)**
- **Pancreatitis (elevated serum amylase level – decreased renal clearance**
- **Cholecystokinine, glucagon are also elevated (increased secretion, decreased metabolism?)**
- **Ascites**

Gastrointestinal-renal syndromes: disorders that may cause gut and kidney disease

Disorder	Kidney	Gut	Symptoms
Polycystic kidney disease	Chronic renal failure, intracyst infection, and hemorrhage	Hepatic cystic change, gastric compression, ascites, splenomegaly, portal hypertension, hernias	Abdominal pain, distention, early satiety
Amyloidosis	Chronic renal failure, nephrotic syndrome	Malabsorption, splenic rupture	Diarrhea, weight loss, melena, acute abdomen
Systemic vasculitis	Proliferative glomerulonephritis	Mesenteric ischemia/infarction, strictures, intussusception	Abdominal pain, diarrhea, GI bleeding, peritonitis
Fabry's disease	Proteinuria, microhematuria, chronic renal failure	Autonomic dysfunction, skin angiokeratomas in bathing trunk area	Recurrent abdominal pain, episodic diarrhea and constipation
Scleroderma	Acute renal failure, chronic renal failure	Distended loops of bowel, small bowel bacterial overgrowth	Dysphagia constipation, abdominal distention, steatorrhea
Diabetes	Chronic renal failure, nephrotic syndrome	Autonomic gastropathy and enteropathy, increased incidence of celiac disease	Episodic vomiting, painless nocturnal watery diarrhea, weight loss
Ulcerative colitis	Chronic renal failure due to AA amyloidosis or sulfasalazine (Salazopyrin)-induced tubulointerstitial nephritis	Colitis, sclerosing cholangitis	Abdominal pain, diarrhea, melena jaundice
Chronic pancreatitis, small bowel disorders	Renal failure due to oxalate-induced nephrolithiasis and tubulointerstitial nephritis	Increased intestinal oxalate absorption	Upper abdominal pain radiating to the back, steatorrhea
Anorexia nervosa, bulimia, laxative or diuretic abuse	Hypokalemic nephropathy, chronic renal failure	Scaphoid abdomen, dental erosions, melanosis coli	Muscle weakness, recurrent vomiting, malnutrition
TRAPS	Nephrotic syndrome, CKD	Serositis	Recurrent abdominal pain, skin rash
Familial Mediterranean fever	Nephrotic syndrome, CKD	Serositis	Recurrent abdominal pain, skin rash
Chronic alcoholism	Secondary IgA nephropathy, hepatorenal syndrome	Esophageal varices, pancreatitis, cirrhosis, ascites	GI hemorrhage, abdominal distention
Nutcracker syndrome	Dilated left renal vain	Acute aortomesenteric angle, left-sided varicocele	Hematuria, proteinuria
Antiphospholipid syndrome	Chronic GN	Adrenal infarction and hemorrhage	Acute abdominal pain, hypotension

Figure 77.2 Gastrointestinal-renal syndromes: disorders that may cause gut and kidney disease. CKD, chronic kidney disease; GI, gastrointestinal; GN, glomerulonephritis; TRAPS, tumor necrosis factor receptor-1–associated fever syndrome.

Dialysis-induced gastrointestinal disorders	
Disorder	Clinical Setting
Nonocclusive mesenteric infarction	Excessive ultrafiltration with intradialytic hypotension in elderly patients
β_2-microglobulin amyloidosis with visceral involvement	Long-term dialysis patients; may cause decreased motility, gastric dilatation, colonic necrosis, melena
Idiopathic (nephrogenic) ascites	Diagnosis of exclusion, rare with modern dialysis
Gastrointestinal hemorrhage	Predominantly elderly hemodialysis patients
Pseudoperitonitis	Icodextrin in peritoneal dialysis patients
Encapsulating peritoneal sclerosis	Long-term peritoneal dialysis, although 30% of cases follow bacterial peritonitis
Hemoperitoneum	Peritoneal dialysis, endometriosis
Dialysate infusion pain	Acidic dialysate, catheter malposition
Scrotal/labial swelling	Peritoneal dialysis patient with patent processus vaginalis or dissection through peritoneal membrane
Infectious peritonitis	Peritoneal dialysis

Figure 77.5 Dialysis-induced gastrointestinal disorders.

Immunologic and Infectious Complications

- **Infection is a common cause of death in CKD**

- **Decreased cellular and humoral defenses**
  a/. granulocyte counts, total immunoglobulin level, complement level are normal
  b/. polymorphonuclear leukocyte, T-cell, B-cell functions are impaired

- **Antibody responses, cell-mediated, immune, chemotactic, phagocytic abnormalities are present (mild)**
  Pruritis – skin infection
  Dialysis – vascular and peritoneal accesses infection
  Delayed wound healing: postoperative, posttraumatic infection

- **Diminished immunity: predisposition to fungal and viral infection**

Abnormalities in Endocrine Function

Uremia alters many hormones (either in amount or in their effects)

- **Decreased renal clearance**
- **Altered receptor activity**
- **Altered protein binding**
- **Interference with feedback controls**

Abnormalities in Endocrine Function

- **Parathyroid glands**
  Increased level of calcitonin (decreased clearance)

- **Thyroid gland:**
  normal free T4, TSH, low free T3 level (diminished conversion T4 to T3 in periphery)

- **Gonadal dysfunction (menstrual irregularities, amenorrhea, conception and ability to complete a pregnancy are impaired):**
  gonadal resistance to FSH, LH
  complex hypothalamic-pituitary disturbances
  hyperprolactinemia

Men: ↓ testosterone

Women: ↓progesterone and estrogen

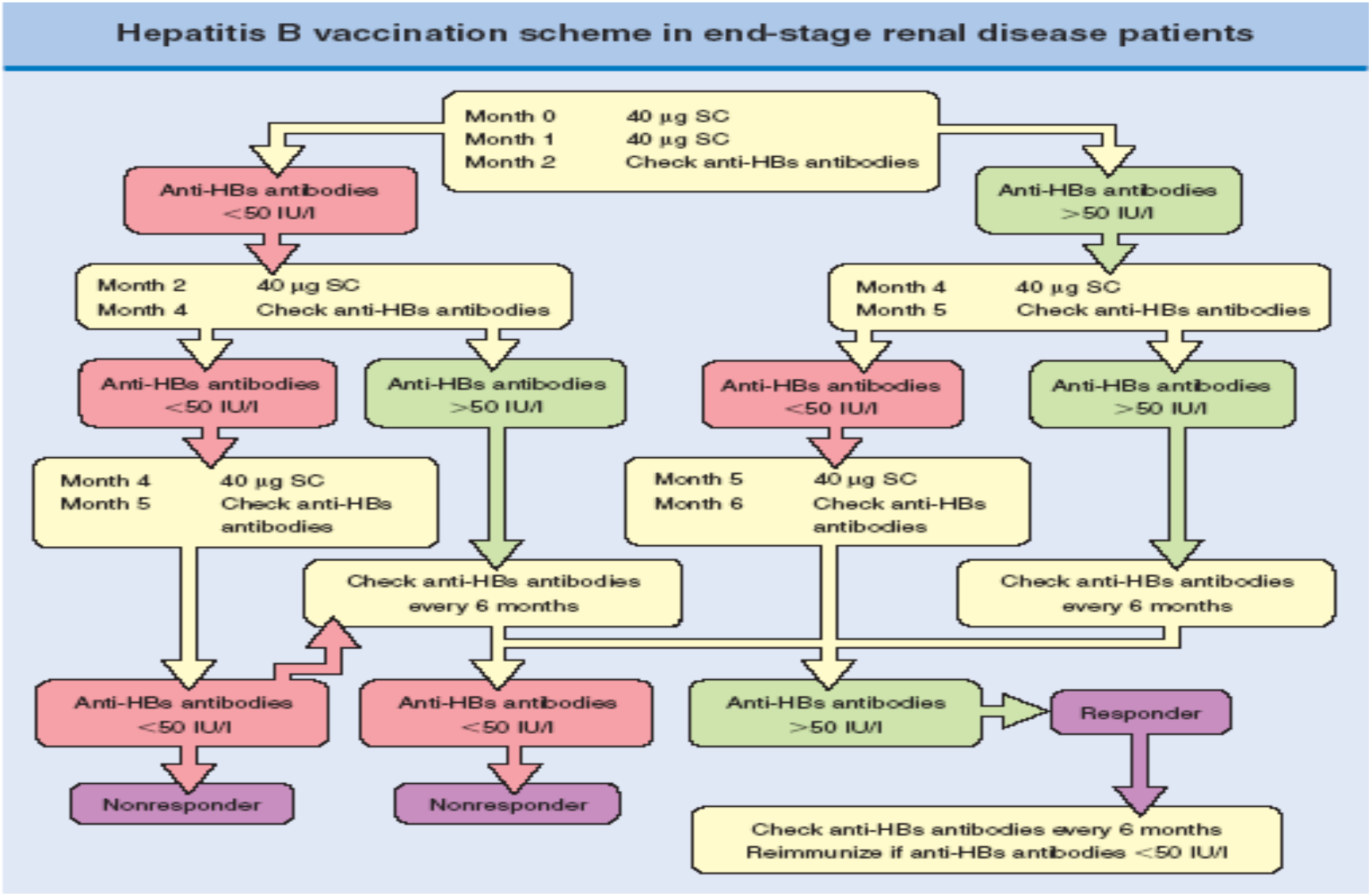


Figure 73.5 Hepatitis B vaccination scheme in end-stage renal disease patients. All patients receive 3 doses of hepatitis B vaccine 40 *µg* SC. An additional dose is given if anti-HBs antibody response is <50 IU/l.