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TITLE: **CHRONIC RENAL FAILURE**

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CHRONIC RENAL FAILURE

Definition

Chronic renal failure (CRF) is a clinical-laboratory syndrome, which results from progressive and irreversible destruction of nephrons, because of a chronic nephropathy.

Etiology

Chronic glomerulonephritis in its several forms was the most common initiating cause of CRF in the past. Possibly because of more aggressive treatment of glomerulonephritis, diabetes mellitus and hypertensive renal disease are now the leading causes of CRF. Diabetes and hypertension are much more prevalent among Asian and African-Caribbean population than among Caucasians, and lead to a much higher incidence of end-stage renal failure in these populations.

Other less often causes of CRF are ADPKD, chronic pyelone-phritis, BEN, chronic interstitial nephritis, satellite nephropathies.

Pathogenesis

Irrespective of cause, the eventual impact of **severe reduction in nephron mass** is an alteration in function of virtually every organ system in the body.

The mechanisms of nephron lesions are: immunologic – autoimmune and immune-complex, inflammatory, mechanical.

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF CRF

The renal function includes five basic elements – depuration of end products of human metabolism, support of a steady composition of body ions and solutions, support of a steady volume of body water, support of steady pH, endocrine function.

a) The finding that sera from patients with ***UREMIA*** exert toxic effects in a variety of biologic test systems has motivated an attempt to identify the responsible toxin(s) – uremic toxin.

Table 1. Uremic "toxins"

Products of protein metabolism

- Guanidino compounds

Guanidine

Methylguanidine

Creatine and creatinine

Guanidinosuccinic acid

- Urates and hyppurates
- End-products of nucleic acid metabolism

- End-products of aliphate amine metabolism
- End-products of aromatic amine acid metabolism

Tryptophane, Tyrosine, Phenylalanine

- Other nitrogenous substances

Polyamines, Myoinositol, Phenols, Benzoates, Indoles

- Advanced glication end products
- Inhibitors of ligand protein binding
- Glucuronoconjugates and alcoves
- Inchibitors of somatomedin and insulin action

b) WATER BALANCE . The normal plasma osmolality is 275 to 290 mosm/L. To maintain a steady state, water intake must equal water excretion. Disorders of water homeostasis result in hypo- or hypernatremia. Normal individuals have an obligate water loss consisting of urine, stool , and evaporation from the skin and respiratory tract. Normally, about 600 mosmols must be excreted per day, and since the maximal urine osmolality is 1200 mosmol/kg a minimum urine output of 500 ml/d is required for neutral solute balance.

c) CRF is likely to lead to abnormally high intracellular Na^+ concentrations and hence to osmotically induced overhydration of cells, whereas these same cells are relatively deficient in K^+. Owing to the *concomitant tendency for salt and water retention* due to impaired excretion, these losses often go unnoticed until the late stages of CRF. Because a large fraction of *the increase in total body water* in uremia is the result of expansion of intracellular volume, extracellular volume also expands.

Deficits in intracellular K^+ concentration in CRF may result from inadequate intake, excessive losses (vomiting, diarrhea, diuretics). *Despite deficits in intracellular K^+, serum K^+ is usually normal or high* in CRF, owing to metabolic acidosis, which induces an efflux of K^+ from cells.

d) With advancing renal failure, total daily acid excretion and buffer production fall below the level needed to maintain external balance of hydrogen ions. Metabolic acidosis is the inevitable result.

Metabolic acidosis can occur because of a loss of bicarbonate, or accumulation of endogenous acids.

e) A *deficit of Vitamin D* with a significant increment in plasma parathyroid hormone was observed early in the course of 157 patients with chronic renal failure. The hyperparathyroidism developed early in the course of chronic renal failure at a time when plasma concentrations of

calcium and phosphorus were still within normal limits, but it could be ameliorated by phosphorus restriction and calcium supplementation.

CLINICAL PRESENTATION OF CRF

Chronic renal failure is associated with a constellation of signs and symptoms, which may or may not include *reduced urine output* but always include *elevation in serum urea nitrogen and creatinine* concentrations. Elevations of serum urea nitrogen and creatinine levels occur late in the course of renal failure.

The severity of signs and symptoms of uremia vary from patient to patient, depending at least in part, on the magnitude of the reduction in functioning renal mass and the rapidity with which renal function is lost. In the relatively early stage of CRF-i.e., when total glomerular filtration rate (GFR) is reduced to about 35 to 50 % of normal - overall renal function is sufficient to keep the patient symptom-free, although renal reserve is diminished.

With further loss of nephron mass (GFR below approximately 20 % of normal), the patient develops *overt renal failure*. Uremia may be viewed as the final stage in this inexorable process, when many or all of the untoward manifestations of CRF become evident clinically and biochemically.

CLASSIFICATION OF CRF

	I grade	**II grade**	**III grade**	**IV grade**
serum creatinine /mcmol/l/	150 - 350	350 - 700	700 - 1300	over 1300
serum urea / mmol/l /	8 - 15	15 - 30	30 - 50	over 50
creatinine clearance /ml/min/	40 - 20	20 - 10	10 - 5	less 5
concentration ability	hypostenuria	isostenuria	isostenuria	isostenuria
diuresis	polyuria	pseudo-normouria	oliguria	oliguria anuria

CRF leads to disturbances in function of every organ and system.

The skin may show evidence of anemia (pallor), defective hemostasis (ecchymoses and hematomas), calcium deposition and secondary hyperparathyroidism (pruritus, excoriations), dehydration (poor skin turgor, dry mucous membranes), and the general cutaneous consequences of protein-calorie malnutrition.

In advanced uremia, the concentration of urea in sweat may be so high that, after evaporation, a fine white powder can be found on the skin surface□so-called *uremic (urea) frost*. Hemochromatosis causes a slate gray to bronze discoloration of the skin and is now uncommon in dialysis patients because of reduced transfusion requirements.

In most patients with stable CRF, the total body contents of Na^+ and water are increased modestly, although expansion of the extracellular fluid (ECF) volume may not be apparent. With ingestion of excessive amounts of salt and water, however, control of excess volume becomes an important consideration***. In general, excessive salt ingestion contributes to or aggravates congestive heart failure, hypertension, ascites, and edema.***

Derangements in K^+ balance are rarely responsible for clinical symptoms unless the GFR is below 10 ml/min or unless an endogenous K^+ load (owing to hemolysis, trauma, infection) or an exogenous one (owing to administration of stored blood or K^+-containing medications) enters the system. ***Hyperkalemia*****.** Not surprisingly, oliguria or disruption of key adaptive mechanisms can lead to hyperkalemia and its potentially ominous effects on cardiac function.

Metabolic Acidosis has profound effects on the respiratory, cardiac, and nervous systems. The fall in blood pH is accompanied by a characteristic increase in ventilation, especially tidal volume (Kussmaul respiration).

Hypertension is the most common symptom of end-stage renal disease. When it is not found, the patient either has a salt-wasting form of renal disease, is receiving antihypertensive therapy, or is volume-depleted. **Since fluid overload is the major cause of hypertension in uremia, the normotensive state can usually be restored by aggressive ultrafiltration with dialysis.**

Pericarditis. Retained metabolic toxins are thought to be the cause of uremic pericarditis. Once a common complication of CRF, pericarditis is now infrequent because of early initiation of dialysis. The clinical presentation of pericarditis in uremic subjects is similar to that seen in nonuremic subjects, except that effusions are usually hemorrhagic.

GASTROINTESTINAL SYNDROME. Anorexia, hiccups, nausea, and vomiting are common early manifestations of uremia. Protein restriction is useful in diminishing nausea and vomiting late in the course of renal failure. However, protein restriction should not be implemented in patients with early signs of protein-calorie malnutrition. *Uremic fetor*, a uriniferous odor to the breath, derives from the breakdown of urea in saliva to ammonia and is often associated with an unpleasant metallic taste sensation. *Mucosal ulcerations* leading to blood loss can occur at any

level of the gastrointestinal tract in the very late stages of CRF. Peptic ulcer disease is common in uremic patients. Whether this high incidence is related to altered gastric acidity, enhanced colonization by

Uremic encephalopathy is variable in its severity. Subtle disturbances of central nervous system function, including inability to concentrate, drowsiness, and insomnia, are among the early symptoms of uremia. Mild behavioral changes, loss of memory, and errors in judgment soon follow and may be associated with neuromuscular irritability, including hiccups, cramps, and fasciculations and twitching of muscles. Asterixis, myoclonus, and chorea are common in terminal uremia, as are stupor, seizures, and coma.

Peripheral neuropathy is also common in advanced CRF. Initially, sensory nerves are involved more than motor nerves, the lower extremities more than the upper, and the distal portions of the extremities more than the proximal. The "restless legs syndrome" is characterized by ill-defined sensations of discomfort in the feet and lower legs and frequent leg movement.

ENDOCRINE-METABOLIC DISTURBANCES

Renal osteodystrophy and *metabolic bone disease* are terms that encompass a number of skeletal abnormalities, including osteomalacia, osteitis fibrosa cystica, and, in children, impaired bone growth. Adynamic or aplastic bone disease is a recently described condition that is detected primarily on bone biopsy, which reveals a reduction in osteoid as well as fibrosis.

Secondary hyperparathyroidism and osteitis fibrosa cystica are more common in children than in adults and are especially common in patients with slowly progressive renal insufficiency.

With osteitis fibrosa cystica, vitamin D-deficient osteomalacia, patients are prone to spontaneous fractures, which are slow to heal. The ribs are most commonly involved in the case of osteitis fibrosa cystica.

Bone pain, even in the absence of fractures, is common in all of the above disorders. In CRF, there is a tendency *to extraosseous or metastatic calcification* when the calcium-phosphorus product is very high (□70). Medium-sized blood vessels, the subcutaneous, articular, and periarticular tissues, the myocardium, the eyes, and the lungs are common sites of metastatic calcification.

Normochromic, normocytic anemia. Erythropoiesis is depressed in CRF, owing to the effects of retained toxins on bone marrow, to *diminished biosynthesis of erythropoietin* by the diseased kidney. Hemolysis is a minor component of uremic anemia.

Table 2. Clinical presentation of CRF

Skin

- Pruritus
- Retarded wound healing
- Dystrophic calcifications
- Melanosis
- Nail atrophy

Pulmonary system

- Uremic lung - pneumonitis
- Pleuritis
- Pulmonary edema

Cardiovascular system

- Atherosclerosis
- Edema
- Decreased diastolic compliance
- Pericarditis
- Hypertension
- Cardiomyopathy
- Hypotension

Gastrointestinal system

- Anorexia, nausea, vomiting
- Stomatitits, gingivitis
- Parotitis
- Gastritis
- Pancreatitis
- Gastrointestinal ulcers
- Enterocolitis
- Ascites

Nervous system-central

- Malaise
- Insomnia
- Headache
- Flipping tremor
- Concentration disturbances
- Drowsiness
- Irritability
- Dementia
- Stupor, coma

Nervous system-peripheral

- Polyneuritis (dysestesia)
- Restless legs
- Singultus (hiccup)
- Convulsions
- Motor weakness
- Fatigue
- Cramps

Endocrinologic

Secondary hyperparathyroidism	Testicular atrophy
Insulin resistance	Ovarian dysfunction – amenorrhea
Hyperlipidemia	Gynecomastia in men
Thyroxine dysmetabolism	

Bone disease

Osteodystrophy	Amyloidosis
Hyperparathyroidism	Calcitriol metabolism defect

Hematological system

Anemia	Bleeding

Miscellaneous

Thirst	Uremic foetor
Weight loss	Hypothermia
Impotence, diminished libido	

DIAGNOSIS

The diagnosis implies that the GFR is known to have been reduced for at least 3 to 6 months. Often a gradual decline in GFR occurs over a period of years.

Proof of chronicity is also provided by the demonstration of *bilateral reduction of kidney size* by ultrasonography. Other findings of long-standing renal failure, such as *renal osteodystrophy* or *symptoms of uremia*, also help to establish this syndrome.

Several laboratory abnormalities are often regarded as reliable indicators of chronicity of renal disease, such as *anemia, hyperphosphatemia, or hypocalcemia*, but these are not specific. Proteinuria is a frequent but nonspecific finding, as is hematuria. DIFFERNTIAL DIAGNOSIS. It can be difficult to differentiate acute from chronic renal failure. The usual *hallmark of CRF is reduced kidney size* as seen by ultrasound scanning or on an abdominal scout film or pyelogram. In the absence of small kidneys, renal biopsy may be necessary for diagnosis.

CONSERVATIVE MANAGEMENT OF CHRONIC RENAL FAILURE

Conservative therapy must be instituted early to control symptoms, minimize complications, prevent long-term sequelae, and slow the progression of renal insufficiency.

a) Etiologic treatment.

Hypertension, urinary tract infections, nephrolithiasis, structural abnormalities of the urinary tract, and the forms of glomeruloneph-ritis that respond to immunosuppressive therapy also should be treated aggressively.

Preventive measures include avoidance of nephrotoxic drugs and radiocontrast agents in patients with compromised renal function. In patients with slowly progressive renal failure, urine output is usually well maintained.

b) Pathogenetic treatment.

DIET**.** In most predialysis patients, a daily *intake of fluid* equal in volume to the urine volume per day plus about 500 ml usually maintains the serum Na^+ concentration at normal levels. In the edematous patient, diuretics and modest restriction of salt and water intake are the mainstays of therapy.

Restriction of dietary *sodium intake* is important in the management of hypertension. As renal insufficiency progresses, foods rich in *phosphate and potassium* should also be restricted. Debate continues as to the clinical usefulness of *lowering the protein content of the diet*. The strongest evidence suggests that this measure is most effective if initiated early in the course of renal failure. Reduction of dietary protein content reduces anorexia, nausea, and vomiting late in uremia. If initiated early (while the GFR is 40 to 50 ml/min), a low-protein diet (0.6 g of protein per kg of body weight) may be effective in slowing the progression of renal disease.

STIMULATION OF RENAL FUNCTION. So called “forced diuresis” may be obtain using salt-water isotonic solutes combined with high doses diuretic – furosemid from 100 up to 1000 mg/daily. The aim is to increase the diuresis over 3 000 ml/day

Correction of acidosis-induced *hyperkalemia* with sodium bicarbonate is the treatment of choice. Intravenous administration of insulin and dextrose, as well are useful in lowering serum K^+ acutely, while the ion exchange resin sodium polystyrene sulfonate (Kayexalate) is the most effective agent in longer-term control of hyperkalemia.

Secondary *hyperparathyroidism* must be treated early to prevent bone disease. Vigorous use of phosphate-binding agents (calcium carbonate and calcium acetate), calcium supplements, and vitamin D (dihydrotachysterol or calcitriol) to maintain the serum levels of calcium (9.5 to 10.5 mg/dl/ 2,4-2,6 mmol/l) and phosphorus (4.5 to 6.0 mg/dl/ 1,4 – 1,9 mmol/l) are often effective in suppressing parathyroid levels and preventing osteitis fibrosa and osteomalacia.

Treatment of anemia includes administration of *recombinant human erythropoietin* as a treatment of choice in patients with advanced renal insufficiency, both before and after initiation of dialysis.

Extracorporeal methods for treatment

The use of chronic dialysis reduces the incidence and severity of disturbances, so that, where modern medicine is practiced, the overt and florid manifestations of uremia have largely disappeared. Unfortunately, even optimal dialysis therapy is not a panacea, because some disturbances resulting from impaired renal function fail to respond fully, while others continue to progress.

Criteria for treatment with hemodialysis or peritoneal dialysis are more liberal *because dialysis has less morbidity than transplantation* in older patients with the aforementioned medical complications.