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The Crux

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CONTENTS

Editorial

ACCEPT OUR HEARTIEST WISHES FOR A VERY HAPPY AND PROSPEROUS NEW YEAR. MAY GOD GRANT PLENTY OF PLEASURES, PROSPERITY AND PEACE OF MIND AND PAUCITY OF PROBLEMS.

Down to earth professional issues, our communiqués will help you in ironing out any professional creases that may have still been left untended. This not so young scientific educational and informational endeavour of ours has completed seven years of existence and we assure you many more happy reading hours for many-many years to come. These issues go to all habitable continents of our earth and are much in demand. We have to consistently increase the number of copies printed almost every month in order to please all our readers. This, of course, is a pleasurable exercise that is covered under the social responsibilities charter of our company. Please visit our website, www.tulipgroup.com and request for your copies of "THE CRUX". We promise to start delivering them to you as soon as possible.

With increasing worries, tensions and sedentary lifestyles – the so-called lifestyle disorders are on the increase. Also increasing longevity of the human life, these disorders are now more visible too. Hypertension and diabetes, both, take a tremendous toll on our kidneys. Unchecked for a long time commences a chronic kidney disease/ or disorder (CKD). The vicious cycle continues – high blood pressure damages kidney and a damaged kidney further aggravates high blood pressure. The whole clinico-diagnostic approach vis-à-vis CKD is presented under the DISEASE DIAGNOSIS segment.

INTERPRETATION portion of this issue lays threadbare the utility of PSA and DRE in diagnosing and managing Prostatic cancer. When to start screening for which population groups, how often must you screen. What should be done for the gray zone values, you'll find answers to all such questions in this part of the issue.

We have over the years presented Quality Assurance issues as related to various sub-specialties of a Medical Diagnostic Laboratory. This volume outlines QA / QC related to the Genetic testing protocols. Pre-analytical, analytical and post-analytical guidelines to be followed are covered under TROUBLE SHOOTING.

BOUQUET is lurking somewhere within the covers of this issue. Flip over a few pages to reach it.

Once again happy trouble free diagnosing for this and future years to come!

DISEASE DIAGNOSIS

Chronic kidney disease

Chronic kidney disease (CKD), also known as **chronic renal disease**, is a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function are unspecific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a blood relative with chronic kidney disease. Chronic kidney disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia or pericarditis. Chronic kidney disease is identified by a blood test for creatinine. Higher levels of creatinine indicate a falling glomerular filtration rate and as a result a decreased capability of the kidneys to excrete waste products. Creatinine levels may be normal in the early stages of CKD, and the condition is discovered if urinalysis (testing of a urine sample) shows that the kidney is allowing the loss of protein or red blood cells into the urine. To fully investigate the underlying cause of kidney damage, various forms of medical imaging, blood tests and often renal biopsy (removing a small sample of kidney tissue) are employed to find out if there is a reversible cause for the kidney malfunction. Recent professional guidelines classify the severity of chronic kidney disease in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is also called established chronic kidney disease and is synonymous with the terms end-stage renal disease (ESRD), chronic kidney failure (CKF) or chronic renal failure (CRF). There is no specific treatment unequivocally shown to slow the worsening of chronic kidney disease. If there is an underlying cause to CKD, such as vasculitis, this may be treated directly with treatments aimed to slow the damage. In more advanced stages, treatments may be required for anemia and bone disease. Severe CKD requires one of the forms of renal replacement therapy; this may be a form of dialysis, but ideally constitutes a kidney transplant. Chronic kidney disease (CKD) is a worldwide public health problem and is now recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF).

Stages: Methods of Measurement for CKD: Stages of kidney failure: Chronic kidney failure is measured in five stages, which are calculated using a patient's GFR, or glomerular filtration rate. Stage 1 CKD is mildly diminished renal function, with few overt symptoms. Stages 2 and 3 need increasing levels of supportive care from their medical providers to slow and treat their renal dysfunction. Patients in stages 4 and 5 usually require preparation of the patient towards active treatment in order to survive. Stage 5 CKD is considered a severe illness and requires some form of renal replacement therapy (dialysis) or kidney transplant whenever feasible. All individuals with a Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage. The rationale for including these individuals is that reduction in kidney function to this level or lower represents loss of half or more of the adult level of normal kidney function, which may be associated with a number of complications. All individuals with kidney damage are classified as having chronic kidney disease, irrespective of the level of GFR. The rationale for including individuals with GFR 60 mL/min/1.73 m^2 is that GFR may be sustained at normal or increased levels despite substantial kidney damage and that patients with kidney damage are at increased risk of the two major outcomes of chronic kidney disease: loss of kidney function and development of cardiovascular disease. The loss of protein in the urine is regarded as an independent marker for worsening of renal function and cardiovascular disease. Hence, British guidelines append the letter "P" to the stage of chronic kidney disease if there is significant protein loss. **Stage 1:** Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2). **Stage 2:** Mild reduction in GFR (60-89 mL/min/1.73 m^2). **Stage 3:** Moderate reduction in GFR (30-59 mL/min/1.73 m^2). **Stage 4:** Severe reduction in GFR (15-29 mL/min/1.73 m^2). **Stage 5:** Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis). In stage 1 and stage 2 chronic kidney disease, GFR alone does not clinch the diagnosis. Other markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests, should also be present in establishing a diagnosis of stage 1 and stage 2 chronic kidney disease.

Pathophysiology: Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR. Regardless of the etiology of renal injury, with progressive destruction of nephrons, the kidney has an innate ability to maintain GFR by hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued normal clearance of plasma solutes so that substances such as urea and creatinine start to show significant increases in plasma levels only after total GFR has decreased to 50%, when the renal reserve has been exhausted. The plasma creatinine value will approximately double with a 50% reduction in GFR. A rise in plasma creatinine from a baseline value of 0.6 mg/dL to 1.2 mg/dL in a patient, although still within the reference range, actually represents a loss of 50% of functioning nephron mass. The residual nephron hyperfiltration and hypertrophy, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. This is believed to occur because of increased glomerular capillary pressure, which damages the capillaries and leads initially to focal and segmental glomerulosclerosis and eventually to global glomerulosclerosis. This hypothesis has been based on studies of five-sixths nephrectomized rats, which develop lesions that are identical to those observed in humans with chronic kidney disease. Factors other than the underlying disease process and glomerular hypertension that may cause progressive renal injury include the following: Systemic hypertension, Acute insults from nephrotoxins or decreased perfusion, Proteinuria, Increased renal ammoniagenesis with interstitial injury, Hyperlipidemia, Hyperphosphatemia with calcium phosphate deposition, Decreased levels of nitrous oxide, Smoking.

Frequency: This increase in CKD is partially explained by the increase in the prevalence of diabetes and hypertension, the two most common causes of chronic kidney disease.

International: The incidence rates of end-stage renal disease (ESRD) have increased steadily internationally since 1989. The United States has the highest incident rate of ESRD, followed by Japan. Japan has the highest prevalence per million population, with the United States taking second place.

Mortality/Morbidity: Chronic kidney disease is a major cause of morbidity and mortality, particularly at the later stages. Although the diabetic population is at highest risk. The 5-year survival rate for a patient undergoing chronic dialysis is approximately 35%. This is approximately 25% in patients with diabetes. The most common cause of death in the dialysis population is cardiovascular disease. Among patients with ESRD aged 65 years and older, the mortality rates are 6 times higher than in the general population. The highest mortality rate is within the first 6 months of initiating dialysis, which then tends to improve over the next 6 months, before increasing gradually over the next 4 years. The mortality rates associated with hemodialysis are striking and indicate that the life expectancy of patients entering into hemodialysis is markedly shortened. At every age, patients with ESRD on dialysis have significantly increased mortality when compared with nondialysis patients and individuals without kidney disease. At age 60 years, a healthy person can expect to live for more than 20 years, whereas the life expectancy of a 60-year-old patient starting hemodialysis is closer to 4 years.

Race: Chronic kidney disease affects all races, but is higher in the coloured races as compared to that for whites.

Sex: Incidence of the chronic kidney disease stages is similar in both sexes.

Age: Chronic kidney disease is found in persons of all ages. The normal annual mean decline in the GFR with age from the peak GFR (approximately 120 mL/min/1.73 m^2) attained during the third decade of life is approximately 1mL/min/y/1.73 m^2, reaching a mean value of 70 mL/min/1.73 m^2 at age 70 years. Nonetheless, internationally, overall, the highest incidence rate of ESRD occurs in patients older than 65 years. Besides diabetes mellitus and hypertension, age is an independent major predictor of chronic kidney disease. The geriatric population is the most rapidly growing kidney failure (chronic kidney disease stage 5) population in the United States. The biologic process of aging initiates various structural and functional changes within the kidney. Renal mass progressively declines with advancing age. Glomerulosclerosis leads to a decrease in renal weight. Histologic examination is notable for a decrease in

glomerular number of as much as 30-50% by age 70 years. Ischemic obsolescence of cortical glomeruli is predominant, with relative sparing of the renal medulla. Juxtamedullary glomeruli see a shunting of blood from the afferent to efferent arterioles, resulting in redistribution of blood flow favoring the renal medulla. These anatomical and functional changes in renal vasculature appear to contribute to an age-related decrease in renal blood flow. Renal hemodynamic measurements in aged human and animals suggest that altered functional response of the renal vasculature may be an underlying factor in diminished renal blood flow and increased filtration noted with progressive renal aging. The vasodilatory response is blunted in the elderly when compared to younger patients. However, the vasoconstrictor response to intrarenal angiotensin is identical in both young and older human subjects. A blunted vasodilatory capacity with appropriate vasoconstrictor response may indicate that the aged kidney is in a state of vasodilatation to compensate for the underlying sclerotic damage. Given the histologic evidence for nephronal senescence with age, a decline in the GFR is expected. However, a wide variation in the rate of decline in the GFR is reported because of measurement methods, race, gender, genetic variance, and other risk factors for renal dysfunction. Because of these anatomical and physiological changes, elderly patients with chronic kidney disease may behave differently, in terms of progression and response to pharmacological treatment, than younger patients.

Therefore, a serum creatinine value of 1.2 mg/dL in a 70-kg, 25-year-old man versus a 70-kg, 80-year-old man represents an eGFR of 74 mL/min/1.73m^2 and 58 mL/min/1.73m^2, respectively. What can appear as only mild renal impairment in a 70-kg, 80-year-old man with a pathologically elevated serum creatinine of 2 mg/dL actually represents severe renal impairment when the eGFR is calculated to be 32 mL/min/1.73m^2. Therefore, an eGFR must be determined simply by using the Modification of Diet in Renal Disease (MDRD) equation (see Other Tests) in elderly people so that appropriate drug dosing adjustments can be made and nephrotoxins can be avoided in patients who have more extensive chronic kidney disease than would be suggested by the serum creatinine value alone.

Clinical History: Patients with chronic kidney disease stages 1-3 (GFR >30 mL/min) are generally asymptomatic and do not experience clinically evident disturbances in water or electrolyte balance or endocrine/metabolic derangements. Generally, these disturbances clinically manifest with chronic kidney disease stages 4-5 (GFR <30 mL/min). Uremic manifestations in patients with chronic kidney disease stage 5 are believed to be primarily secondary to an accumulation of toxins, the identity of which is generally not known. The ability to maintain potassium (K) excretion at near normal levels is generally maintained in chronic kidney disease patients as long as both aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with chronic kidney disease is increased potassium excretion in the GI tract, which also is under control of aldosterone. Therefore, hyperkalemia usually develops when the GFR falls to less than 20-25 mL/min because of the decreased ability of the kidneys to excrete potassium. It can be observed sooner in patients who ingest a potassium-rich diet or if serum aldosterone levels are low, such as in type IV renal tubular acidosis commonly observed in people with diabetes or with use of angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs). Hyperkalemia in chronic kidney disease can be aggravated by an extracellular shift of potassium, such as that occurs in the setting of acidemia or from lack of insulin. Hypokalemia is uncommon but can develop among patients with very poor intake of potassium, gastrointestinal or urinary loss of potassium, diarrhea, or diuretic use. Metabolic acidosis often is mixed, normal anion gap and increased anion gap, the latter observed generally with chronic kidney disease stage 5 but with the anion gap generally not higher than 20 mEq/L. In chronic kidney disease, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium. In chronic kidney disease stage 5, accumulation of phosphates, sulphates, and other organic anions are the cause of the increase in anion gap. Metabolic acidosis has been shown to have deleterious effects on protein balance, leading to a negative nitrogen balance, increased protein degradation, increased essential amino acid oxidation, reduced albumin synthesis, and a lack of adaptation to a low protein diet. Hence, this is associated with protein-energy malnutrition, loss of lean body mass, and muscle weakness. The mechanism for reducing protein may include effects on ATP-dependent ubiquitin proteasomes and increased activity of branched chain keto acid dehydrogenases. In a prevalence study, hypoalbuminemia (a marker of protein-energy malnutrition and a powerful predictive marker of mortality in dialysis patients as well as in the general population) was independently associated with low bicarbonate as well as the inflammatory marker C reactive protein. Metabolic acidosis is a factor in the development of renal osteodystrophy, as bone acts as a buffer for excess acid, with resultant loss of mineral. Acidosis may interfere with vitamin D metabolism, and patients who are persistently more acidotic are more likely to have osteomalacia or low-turnover bone disease. The evidence for the benefits and risks of correcting metabolic acidosis is very limited, with no randomized controlled trials in pre-ESRD patients, none in children, and only 3 small trials in dialysis patients. These trials suggest that there may be some beneficial effects on both protein metabolism and bone metabolism, but the trials were underpowered to provide robust evidence. Experts recommend alkali therapy to maintain the serum bicarbonate concentration above 22 mEq/L. Inflammation and hemostasis may increase the risk of kidney function decline, but prospective studies are lacking. The Atherosclerosis Risk in Communities Study, a prospective observational cohort, observed markers of inflammation and hemostasis in 14,854 middle-aged adults. The risk for decreased kidney function associated with the inflammatory and hemostasis markers was examined, using data from 1787 cases of chronic kidney disease (CKD) that developed between 1987 and 2004. After adjustments for various factors, such as demographics smoking, blood pressure, diabetes, lipid levels, prior myocardial infarction (MI), antihypertensive use, and alcohol use, the above study revealed that the risk for chronic kidney disease rose with increasing quartiles of white blood cell (WBC) count, fibrinogen, von Willebrand factor, and factor VIIIc. The investigators found a strong inverse association between serum albumin level and chronic kidney disease risk. The study's findings suggested that inflammation and hemostasis are antecedent pathways for chronic kidney disease. Salt and water handling by the kidney is altered in patients with chronic kidney disease. Extracellular volume expansion and total-body volume overload results from failure of sodium and free water excretion. This generally becomes clinically manifested when the GFR falls to less than 10-15 mL/min, when compensatory mechanisms have become exhausted. As kidney function declines further, sodium retention and extracellular volume expansion lead to peripheral and, not uncommonly, pulmonary edema and hypertension. At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion. Normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. It starts early in the course of disease and becomes more severe as the GFR progressively decreases with the availability of less viable renal mass. No reticulocyte response occurs. RBC survival is decreased, and tendency of bleeding is increased from the uremia-induced platelet dysfunction. Other causes of anemia in chronic kidney disease patients include chronic blood loss, secondary hyperparathyroidism, inflammation, nutritional deficiency, and accumulation of inhibitors of erythropoiesis. Anemia is associated with fatigue, reduced exercise capacity, impaired cognitive and immune function, and reduced quality of life. Anemia is also associated with the development of cardiovascular disease, the new onset of heart failure, or the development of more severe heart failure. Anemia is associated with increased cardiovascular mortality. Renal bone disease is a common complication of chronic kidney disease and results in both skeletal complications (eg, abnormality of bone turnover, mineralization, linear growth) and extraskeletal complications (eg, vascular or soft tissue calcification). Different types of bone disease occur with chronic kidney disease, as follows: (1) high turnover bone disease due to high parathyroid hormone (PTH) levels; (2a) low turnover bone disease (adynamic bone disease); (2b) defective mineralization (osteomalacia); (3) mixed disease; and (4) beta-2-microglobulin associated bone disease. Secondary hyperparathyroidism develops because of hyperphosphatemia, hypocalcemia, decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol), intrinsic alteration in the parathyroid gland that give rises to increased PTH secretion as well as increased parathyroid growth, and skeletal resistance to PTH. Calcium and calcitriol are primary feedback inhibitors; hyperphosphatemia is a stimulus to PTH synthesis and

secretion. Phosphate retention begins in early chronic kidney disease; when the GFR falls, less phosphate is filtered and excreted, but serum levels do not rise initially because of increased PTH secretion, which increases renal excretion. As the GFR falls toward chronic kidney disease stages 4-5, hyperphosphatemia develops from the inability of the kidneys to excrete the excess dietary intake. Hyperphosphatemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol, so serum calcitriol levels are low when the GFR is less than 30 mL/min. Increased phosphate concentration also effects PTH concentration by its direct effect on parathyroid gland (posttranscriptional effect). Hypocalcemia develops primarily from decreased intestinal calcium absorption because of low plasma calcitriol levels and possibly from calcium binding to elevated serum levels of phosphate. Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and secretion. As these stimuli persist in chronic kidney disease, particularly in the more advanced stages, PTH secretion becomes maladaptive and the parathyroid glands, which initially hypertrophy, become hyperplastic. The persistently elevated PTH levels exacerbate hyperphosphatemia from bone resorption of phosphate. If serum levels of PTH remain elevated, a high bone turnover lesion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as renal osteodystrophy. These lesions develop in patients with severe chronic kidney disease and are common in those with ESRD. The prevalence of adynamic bone disease has increased, and it has been described before the initiation of dialysis in some cases. The pathogenesis of adynamic bone disease is not well defined, but several factors may contribute, including high calcium load, use of vitamin D sterols, increasing age, previous corticosteroid therapy, peritoneal dialysis, and increased level of N-terminally truncated PTH fragments. Low turnover osteomalacia in the setting of chronic kidney disease is associated with aluminum accumulation and is markedly less common. Dialysis-related amyloidosis from beta-2-microglobulin accumulation in patients who have required chronic dialysis for at least 8-10 years is another form of bone disease that manifests with cysts at the ends of long bones. Other manifestations of uremia in ESRD, many of which are more likely in patients who are inadequately dialyzed, include the following: Pericarditis - Can be complicated by cardiac tamponade, possibly resulting in death. Encephalopathy - Can progress to coma and death. Peripheral neuropathy. Restless leg syndrome. GI symptoms - Anorexia, nausea, vomiting, diarrhea. Skin manifestations - Dry skin, pruritus, ecchymosis. Fatigue, increased somnolence, failure to thrive. Malnutrition. Erectile dysfunction, decreased libido, amenorrhea. Platelet dysfunction with tendency to bleeding.

Physical: The physical examination often is not very helpful but may reveal findings characteristic of the condition underlying chronic kidney disease (eg, lupus, severe arteriosclerosis, hypertension) or complications of chronic kidney disease (eg, anemia, bleeding diathesis, pericarditis).

Symptoms: Symptoms can vary from person to person. Someone in early stage kidney disease may not feel sick or notice symptoms as they occur. When kidneys fail to filter properly, waste accumulates in the blood and the body, a condition called azotemia. Very low levels of azotaemia may produce few, if any, symptoms. If the disease progresses, symptoms become noticeable (if the failure is of sufficient degree to cause symptoms). Renal failure accompanied by noticeable symptoms is termed uraemia. **Symptoms of kidney failure include:** High levels of urea in the blood, which can result in: Vomiting and/or diarrhea, which may lead to dehydration, Nausea, Weight loss, Nocturnal urination, Foamy or bubbly urine, More frequent urination, or in greater amounts than usual, with pale urine, Less frequent urination, or in smaller amounts than usual, with dark coloured urine, Blood in the urine, Pressure, or difficulty urinating. A build up of phosphates in the blood that diseased kidneys cannot filter out may cause: Itching, Bone damage, Muscle cramps (caused by low levels of calcium which can cause hypocalcaemia). A build up of potassium in the blood that diseased kidneys cannot filter out (called hyperkalemia) may cause: Abnormal heart rhythms, Muscle paralysis. Failure of kidneys to remove excess fluid may cause: Swelling of the legs, ankles, feet, face and/or hands, Shortness of breath due to extra fluid on the lungs (may also be caused by anemia). Polycystic kidney disease, which causes large, fluid-filled cysts on the kidneys and sometimes the liver, can cause: Pain in the back or side. Healthy kidneys produce the hormone erythropoietin which stimulates the bone marrow to make oxygen-carrying red blood cells. As the kidneys fail, they produce less erythropoietin, resulting in decreased production of red blood cells to replace the natural breakdown of old red blood cells. As a result, the blood carries less hemoglobin, a condition known as anemia. This can result in: Feeling tired and/or weak, Memory problems, Difficulty concentrating, Dizziness, Low blood pressure. Other symptoms include: Appetite loss, a bad taste in the mouth, Difficulty sleeping, Darkening of the skin.

Causes: Vascular disease - Renal artery stenosis, cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)–positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)–positive vasculitides, antineutrophil cytoplasmic antibody (ANCA)–negative vasculitides, atheroemboli, hypertensive nephrosclerosis, renal vein thrombosis. Primary glomerular disease - Membranous nephropathy, immunoglobulin A (IgA) nephropathy, focal and segmental glomerulosclerosis (FSGS), minimal change disease, membranoproliferative glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis. Secondary glomerular disease - Diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, scleroderma, Goodpasture syndrome, Wegener granulomatosis, mixed cryoglobulinemia, postinfectious glomerulonephritis, endocarditis, hepatitis B and C, syphilis, human immunodeficiency virus (HIV), parasitic infection, heroin use, gold, penicillamine, amyloidosis, light chain deposition disease, neoplasia, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), Henoch-Schönlein purpura, Alport syndrome, reflux nephropathy. Tubulointerstitial disease - Drugs (eg, sulfa, allopurinol), infection (viral, bacterial, parasitic), Sjögren syndrome, chronic hypokalemia, chronic hypercalcemia, sarcoidosis, multiple myeloma cast nephropathy, heavy metals, radiation nephritis, polycystic kidneys, cystinosis. Urinary tract obstruction - Urolithiasis, benign prostatic hypertrophy, tumors, retroperitoneal fibrosis, urethral stricture, neurogenic bladder.

Laboratory Studies: Diagnostic approach: Glomerular filtration rate: A normal GFR varies according to many factors, including sex, age, body size and ethnicity. Renal professionals consider the glomerular filtration rate (GFR) to be the best overall index of kidney function. A serum creatinine level, a simple blood test, is needed to use the GFR calculation. A RECENT MARKER IS CYSTATIN C that asseses renal function better. Serum electrolytes, BUN, and creatinine - The BUN and creatinine levels will be elevated in patients with chronic kidney disease. Hyperkalemia or low bicarbonate levels may be present in patients with chronic kidney disease. Serum calcium, phosphate, vitamin D, and intact parathyroid hormone (PTH) levels are obtained to look for evidence of renal bone disease. CBC count - Normochromic normocytic anemia is commonly seen in chronic kidney disease. Other underlying causes of anemia should be ruled out. Serum albumin - Patients may have hypoalbuminemia due to urinary protein loss or malnutrition. Lipid profile - A lipid profile should be performed in all patients with chronic kidney disease because of their increased risk of cardiovascular disease. Urinalysis - Dipstick proteinuria may suggest a glomerular or tubulointerstitial problem. The urine sediment finding of RBCs, RBC casts, suggests proliferative glomerulonephritis. Pyuria and/or WBC casts are suggestive of interstitial nephritis (particularly if eosinophiluria is present) or urinary tract infection. Spot urine collection for total protein-to-creatinine ratio allows reliable approximation (extrapolation) of total 24-hour urinary protein excretion. A value of greater than 2 g is considered to be within the glomerular range, and a value of greater than 3-3.5 g is within the nephrotic range; less than 2 is characteristic of tubulointerstitial problems. Twenty-four–hour urine collection for total protein and CrCl. In certain cases, the following tests may be ordered as part of the evaluation of patients with chronic kidney disease: Serum and urine protein electrophoresis to screen for a monoclonal protein possibly representing multiple myeloma, Antinuclear antibodies (ANA), double-stranded DNA antibody levels to screen for systemic lupus erythematosus, Serum complement levels - May be depressed with some glomerulonephritides, C-ANCA and P-ANCA levels - Helpful if positive in diagnosis of Wegener granulomatosis and polyarteritis nodosa or microscopic polyangiitis, respectively, Anti–glomerular basement membrane (anti-GBM) antibodies - Highly suggestive of underlying Goodpasture syndrome, Hepatitis B and C, HIV, Venereal Disease Research Laboratory (VDRL) serology - Conditions associated with some glomerulonephritides.

Imaging Studies: Plain abdominal x-ray - Particularly useful to look for radio-opaque stones or nephrocalcinosis. Intravenous pyelogram - Not commonly

used because of potential for intravenous contrast renal toxicity; often used to diagnose renal stones. Renal ultrasound - Small echogenic kidneys are observed in advanced renal failure. Kidneys usually are normal in size in advanced diabetic nephropathy, where affected kidneys initially are enlarged from hyperfiltration. Structural abnormalities, such as polycystic kidneys, also may be observed. This is a useful test to screen for hydronephrosis, which may not be observed in early obstruction, or involvement of the retroperitoneum with fibrosis, tumor, or diffuse adenopathy. Retrograde pyelogram may be indicated if a high index of clinical suspicion for obstruction exists despite a negative study finding. Renal radionuclide scan - Useful to screen for renal artery stenosis when performed with captopril administration but is unreliable for GFR of less than 30 cc/min; also quantitates differential renal contribution to total GFR. CT scan - CT scan is useful to better define renal masses and cysts usually noted on ultrasound. Also, it is the most sensitive test for identifying renal stones. IV contrast-enhanced CT scans should be avoided in patients with renal impairment to avoid acute renal failure; this risk significantly increases in patients with moderate-to-severe chronic kidney disease. Dehydration also markedly increases this risk. MRI is very useful in patients who require a CT scan but who cannot receive intravenous contrast. It is reliable in the diagnosis of renal vein thrombosis, as are CT scan and renal venography. Magnetic resonance angiography also is becoming more useful for diagnosis of renal artery stenosis, although renal arteriography remains the criterion standard. Voiding cystourethrogram (VCUG) - Criterion standard for diagnosis of vesicoureteral reflux.

Other Tests: The Cockcroft-Gault formula for estimating CrCl should be used routinely as a simple means to provide a reliable approximation of residual renal function in all patients with chronic kidney disease. The formulas are as follows: CrCl (male) = ([140-age] X weight in kg)/(serum creatinine X 72), CrCl (female) = CrCl (male) X 0.85. Alternatively, the Modification of Diet in Renal Disease (MDRD) Study equation could be used to calculate the GFR. This equation does not require a patient's weight.

Procedures: Percutaneous renal biopsy is performed most often with ultrasound guidance and the use of a mechanical gun. It generally is indicated when renal impairment and/or proteinuria approaching the nephrotic range are present and the diagnosis is unclear after appropriate other workup. It is not indicated in the setting of small echogenic kidneys on ultrasound because these are severely scarred and represent chronic irreversible injury. The most common complication of this procedure is bleeding, which can be life threatening in a minority of occurrences. Surgical open renal biopsy can be considered when the risk of renal bleeding is felt to be great, occasionally with solitary kidneys, or when percutaneous biopsy is technically difficult to perform.

Histologic Findings: Renal histology in chronic kidney disease reveals findings compatible with the underlying primary renal diagnosis and, generally, findings of segmental and globally sclerosed glomeruli and tubulointerstitial atrophy, often with tubulointerstitial mononuclear infiltrates.

Treatment: Medical Care: The medical care of patients with chronic kidney disease should focus on the following: Delaying or halting the progression of chronic kidney disease - Treatment of the underlying condition if possible. Aggressive blood pressure control to target values per current guidelines. Systolic blood pressure control is considered more important and is also considered difficult to control in elderly patients with chronic kidney disease. Use of ACE inhibitors or angiotensin receptor blockers as tolerated, with close monitoring for renal deterioration and for hyperkalemia (avoid in advanced renal failure, bilateral renal artery stenosis [RAS], RAS in a solitary kidney). Data support the use of ACE inhibitors/angiotensin receptor blockers in diabetic kidney disease with or without proteinuria. However, in nondiabetic kidney disease, ACE inhibitors/angiotensin receptor blockers are effective in retarding the progression of disease among patients with proteinuria of less of than 500 mg/d. Aggressive glycemic control per the American Diabetes Association (ADA) recommendations (target HbA1C <7%). Protein restriction - Although the Modification of Diet in Renal Disease (MDRD) Study failed to show the effect of protein restriction in retardation of the progression of kidney disease, a meta-analysis suggests a beneficial role for protein restriction. The National Kidney Foundation (NKF) of US guidelines suggest that if a patient is started on protein restriction, the physician needs to closely monitor the patient's nutritional status.

Predialysis low serum albumin is associated with a poor outcome among dialysis patients. Treatment of hyperlipidemia to target levels per current guidelines. Avoidance of nephrotoxins - IV radiocontrast, nonsteroidal anti-inflammatory agents, aminoglycosides. Encourage smoking cessation, as smokers tend to reach ESRD earlier than nonsmokers. De Brito-Ashurst et al studied whether bicarbonate supplementation preserves renal function in chronic kidney disease (CKD). Adult patients (n=134) with chronic kidney disease (ie, creatinine clearance [CrCl] 15-30 mL/min/1.73 m^2 and serum bicarbonate 16-20 mmol/L) were randomly assigned to receive oral sodium bicarbonate supplementation or standard care for 2 years. A slower decline in CrCl was observed in the bicarbonate group than in the control group (1.88 vs 5.93 mL/min/1.73 m^2; P <0.0001). Patients in the bicarbonate group were also less likely to experience rapid disease progression than were members of the control group (9% vs 45%; P <0.0001), and fewer patients who received bicarbonate supplementation developed ESRD (6.5% vs 33%; P <0.001). In addition to the benefits listed above, nutritional parameters improved with bicarbonate supplementation. Treating the pathologic manifestations of chronic kidney disease, including the following: Anemia with erythropoietin, with the goal being 11-12 g/dL, as normalization of hemoglobin in patients with chronic kidney disease stages 4-5 has been associated with an increased risk of combined outcome. Before starting Epogen, iron stores should be checked, and the aim is to keep iron saturation at 30-50% and ferritin at 200-500. Hyperphosphatemia with dietary phosphate binders and dietary phosphate restriction. Hypocalcemia with calcium supplements with or without calcitriol. Hyperparathyroidism with calcitriol or vitamin D analogs. Volume overload with loop diuretics or ultrafiltration. Metabolic acidosis with oral alkali supplementation. Uremic manifestations with chronic renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation): Indications include severe metabolic acidosis, hyperkalemia, pericarditis, encephalopathy, intractable volume overload, failure to thrive and malnutrition, peripheral neuropathy, intractable gastrointestinal symptoms, and the GFR less than 10 mL/min. Cardiovascular complications.

Timely planning for chronic renal replacement therapy: Early education regarding natural disease progression, different dialytic modalities, renal transplantation, patient option to refuse or discontinue chronic dialysis. Timely placement of permanent vascular access (arrange for surgical creation of primary arteriovenous fistula, if possible, and preferably at least 6 months in advance of anticipated date of dialysis). Timely elective peritoneal dialysis catheter insertion. Timely referral for renal transplantation.

Diet: Protein restriction early in chronic kidney disease as a means to delay a decline in the GFR is controversial; however, as the patient approaches chronic kidney disease stage 5, this is recommended to delay the onset of uremic symptoms. Patients with chronic kidney disease who already are predisposed to becoming malnourished are at higher risk for malnutrition with overly aggressive protein restriction. Malnutrition is a well-established predictor of increased morbidity and mortality in the ESRD population and must be avoided if possible. Phosphate restriction starting early in chronic kidney disease. Potassium restriction. Sodium and water restriction as needed to avoid volume overload.

Prognosis: The prognosis of patients with chronic kidney disease is guarded as epidemiological data has shown that all cause mortality (the overall death rate) increases as kidney function decreases. The leading cause of death in patients with chronic kidney disease is cardiovascular disease, regardless of whether there is progression to stage 5. While renal replacement therapies can maintain patients indefinitely and prolong life, the quality of life is severely affected. Renal transplantation increases the survival of patients with stage 5 CKD significantly when compared to other therapeutic options, however, it is associated with an increased short-term mortality (due to complications of the surgery). Transplantation aside, high intensity home hemodialysis appears to be associated with improved survival and a greater quality of life, when compared to the conventional three times a week hemodialysis and peritoneal dialysis. Patients with chronic kidney disease generally progress to ESRD. The rate of progression depends on the underlying diagnosis, on the successful implementation of secondary preventative measures, and on the individual patient. Patients on chronic dialysis have a high incidence of morbidity and mortality. Patients with ESRD who undergo renal transplantation survive longer than those on chronic dialysis.

INTERPRETATION

BREAST LUMP ASPIRATION

"Cysts account for about 25% of all breast lumps and are common in premenopausal women over 35 years of age and uncommon in postmenopausal women unless they have received hormone therapy. In this article, we review an approach to the initial management of palpable breast lumps and describe several techniques for breast lump aspiration in the outpatient setting." Women who have a breast lump and features suggesting cancer should be referred to a breast surgeon and immediately undergo mammography, ultrasonography, and core biopsy. These features include hard, irregular mass fixed to the skin; palpable ipsilateral lymph nodes; or a puckered "peau d'orange" appearance of the skin. The family physician can begin in-office workup and management of a palpable breast lump not clinically suspicious for malignant disease. The lump should be aspirated with a fine needle because differentiating cystic from solid lesions using palpation alone can be difficult, and imaging may involve wait time, causing unnecessary anxiety for the patient. However, ultrasound is an alternative initial option to distinguish cystic from solid lumps. Women with breast implants and those receiving anticoagulant therapy should not undergo aspiration in the family physician's office. When aspiration is performed, a local anesthetic is not needed. A simple cyst is diagnosed when aspiration yields nonbloody fluid, and the lump completely disappears. Using clock position and distance from the nipple, the physician should precisely document the cyst's location in the breast, and the fluid may be discarded. However, women should be referred to a surgeon if aspiration yields bloody fluid, if the lump does not disappear completely, or if the lump recurs. In these cases, the aspirate should be sent for pathologic examination by a skilled cytopathologist. When fine-needle insertion indicates that the breast lump is solid, the needle may be removed without further aspiration, or an aspiration biopsy may be performed and the specimen sent for cytopathologic analysis. Complications of aspiration may include local discomfort; bruising caused by blood vessel puncture; transient vasovagal reaction; or, uncommonly, a pneumothorax, which can be avoided by moving a lesion close to the chest wall over a rib before aspiration. However, immediate inspiratory and expiratory chest radiographs are indicated if air is drawn into the syringe. Aspiration is not associated with higher rate of false-positive mammography results if the radiologist is informed about the aspiration site, nor is there any evidence that needle biopsy will cause malignant lesions to spread. Most cancers are diagnosed before surgery by needle or core biopsy. Women who have a simple cyst should be seen in 6 to 8 weeks to be evaluated for recurrence, which, if present, mandates ultrasonography, mammography, or both, as well as surgical referral. No additional workup is needed for cysts that do not recur. Women with solid lesions require imaging and surgical referral. Ultrasonography only is recommended for women younger than 30 years, whereas women at least 30 years old should have both mammography and ultrasonography studies. To ensure concordance between clinical findings and the results of imaging and cytopathologic evaluation of solid breast lumps, triple assessment is recommended (examination, imaging, and aspiration). Some clinicians opt to defer cytopathologic testing of palpable lumps presumed to be fibroadenomas, but this strategy may result in some breast cancers being missed in young women. Most delays in diagnosing breast cancer in this group occur as a result of falsely reassuring clinical or imaging findings. "Aspiration of a palpable breast lump allows immediate reassurance for women with breast cysts and timely investigation and referral for women with solid masses," the review authors conclude. "If the lump is a cyst, the aspirated fluid may be discarded provided the fluid is not bloody and the lump disappears. If the lump is solid, triple assessment (clinical examination, breast imaging and fine-needle aspiration cytologic assessment) is warranted."

BOUQUET

In Lighter Vein

What The Words Really Mean

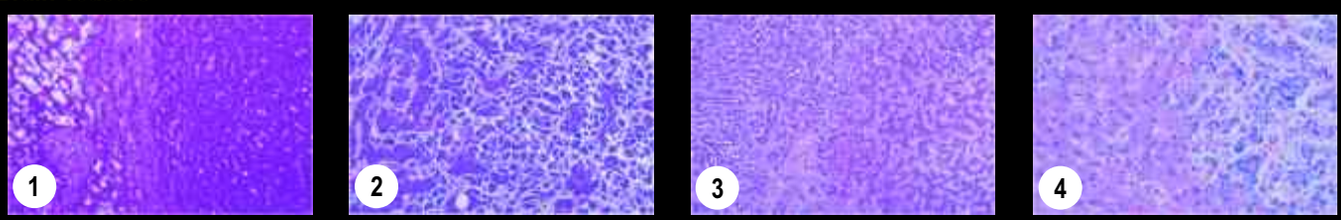
1) Outgoing personality - Always going out of the office
2) Great presentation skills - Able to bullshit
3) Good communication skills - Spends a lot of time on the phone
4) Work is first priority - Too ugly to get a date
5) Active socially - Drinks a lot
6) Independent worker - No one knows what you are doing
7) Quick thinking - Gives excuses on the go
8) Careful thinker - Will not make decisions
9) Uses logic on difficult jobs - Gets someone else to do it
10) Expresses themselves well - Speaks English
11) Meticulous attention to detail - A nit-picker
12) Has leadership qualities - Is tall or has a louder voice
13) Exceptionally good judgment - Has been very lucky
14) Keen sense of humor - Knows a lot of dirty jokes
15) Career minded - Back stabber

Wisdom Whispers

- "What's done is done."
- "Silence is also speech."
- "A man who prides himself on his ancestry is like the potato plant, the best part of which is underground."
- "Few words sufficeth to a wise man."
- "We receive nothing with so much reluctance as advice."
- "Every little blade of grass declares the presence of God."
- "A blind man is not judge of colours."
- "A handful of mother wit is worth a bushel of learning."
- "There are good and bad everywhere."
- "Think late, suffer soon."
- "Fools ask what's o'clock, but wise men know their time."
- "Man concocts a million schemes; God knows but one."

Brain Teasers

Identify the following tumours related to liver



Answers: Fig.1.Hepatic adenoma on the right half, 2. Hepatocellular carcinoma, 3. Cholangiocarcinoma liver on the left of the picture, 4. Metastatic infiltrating duct carcinoma from breast in the liver, seen on the right half.

TROUBLESHOOTING

GENETIC TESTING

An international body - Clinical Laboratory Improvement Advisory Committee (CLIAC) has reviewed quality concerns related to molecular genetic testing. The newly released report reflects CLIAC recommendations of "good laboratory practices for ensuring the quality of molecular genetic testing for heritable diseases and conditions."

History of Genetic Testing Recommendations: This report cites previous studies of clinical laboratory tests in general, showing that more errors originate during preanalytic and postanalytic phases of testing than during the analytic process itself. Inappropriate test selection underlies many preanalytic errors. For example, a study of testing for the adenomatous polyposis coli gene found that in 17% of the cases, testing was unwarranted. "When you talk about errors in laboratory testing, you look at that in the broad sense, where errors can occur anywhere from what goes into the medical decision that the doctor uses in test selection. And that's the practice of medicine, which the guideline does not address," specialists say. "Good laboratory practice, and also part of the general regulatory requirement, is for the laboratory to make available to users information about the tests that they provide," "So the laboratory may be able to influence correct decision-making if physicians work with the laboratory to understand what tests are provided and the characteristics of that test" in terms of answering their questions. "The guideline strives to emphasize that role for laboratory practice but does not cross over that line of medical practice." The CLIAC Genetic Testing Good Laboratory Practices Workgroup evaluated factors in genetic testing likely to affect quality and identified areas in need of quality assurance guidelines to comply with current CLIA requirements. The recommended practices relate specifically to testing for heritable diseases. "We know that genetic testing is growing and is expanding, and so we can't really say for sure how many labs will pick up on it and where the testing will be done," noted a researcher "But the recommendations were set up the way that they were so that, regardless of where this testing is done in the future, if labs are following these recommendations, we could be assured of the quality of the testing, that it was producing accurate results."

Preanalytic Testing Phase Guidelines: In the preanalytic testing phase, the report lists laboratory guidelines for providing information about molecular genetic tests to those who use their services. The information should include: Selection of appropriate tests; Information on proper methods for collecting, handling, transporting, and submitting specimens; Patient information needed for proper testing and reporting of results; Indication of potential implications of the results for family members; and Availability of laboratory consultations regarding the issues mentioned earlier. "What is included in this guidance are elements that users of laboratory services should look for when deciding to engage a laboratory, in terms of good laboratory practice," commented a scientist "[This] would be the laboratory making available to the user of its services information about the test that is offered.... When [physicians] are trying to evaluate laboratory services,...use those criteria to determine whether the test that you are thinking of ordering is actually valid for the purposes that you are ordering it for," emphasized the same scientist. Additional concerns addressed by the work group in the preanalytic phase were informed consent, test requests, specimen handling, and establishing policies to assess and correct problems in the preanalytic phase.

Analytic Testing Phase Guidelines: The analytic phase of molecular genetic testing was already regulated by CLIA requirements to "establish or verify the analytic performance of all non-waived tests and test systems before introducing them for patient testing." Beyond adherence to the more general CLIA requirements, recommendations for molecular and genetic testing focus on the assurance of validity and reliability in the tests and proper interpretation of test results. "Many labs have pretty rigorous assurance quality management systems in place. What's less controlled is the lab's capacity to control or influence what comes to them from clinical settings," "So there are communication issues there sometimes, and [issues] in terms of interpreting results.... While errors are made, the data do suggest that [in] the vast majority of testing, there's not a significant problem that has really been documented." Recommendations regarding establishing and verifying performance specifications for molecular genetic tests list 5 guidelines to be followed for each test: "Conduct a review of available scientific studies and pertinent references, Define appropriate patient populations for which the test should be performed, Select the appropriate test methodology for the disease or condition being evaluated, Establish analytic performance specifications and determine quality control procedures using the appropriate number, type, and variety of samples, Ensure that test results and their implications can be interpreted for an individual patient or family and that the limitations of the test are defined and reported." Studies of the analytic phase of DNA-based genetic testing have reported errors in specimen handling and analysis in only 0.06% to 0.12% of nearly 100,000 tests studied. Recommendations for the analytic phase devote significant attention to control procedures and emphasize the importance of proficiency testing in evaluating laboratory competence (as well as in providing education for lab personnel).

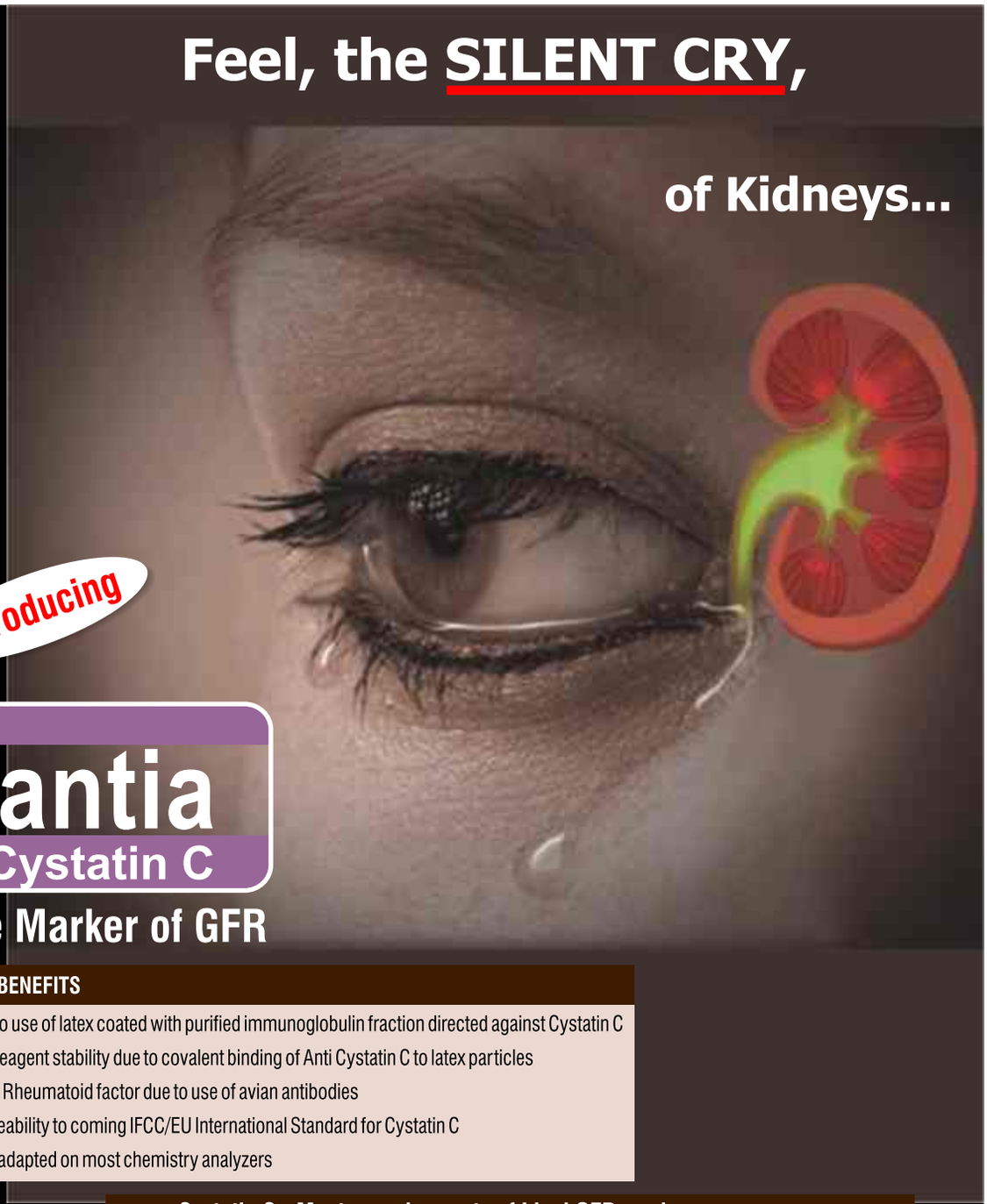
Postanalytic Testing Phase Guidelines: Postanalytic errors commonly reflect problems in preparing reports and interpreting results. Studies have shown that a major contributor to these problems is poor understanding among healthcare providers of the limitations of molecular genetic tests and their proper interpretation. For postanalytic testing, the recommendations focus on content, completeness, and interpretation of test reports. In addition, CLIA requires that test reports, records, and even the tested specimens be retained for specified periods ranging from "as long as possible" for tested specimens to 2 years for test reports and 10 years for pathology test reports. These recommendations recognize the potential importance of these materials for family members and for future diagnostic use, as medical technology and knowledge progress. Finally, the report speaks to issues of confidentiality, laboratory personnel, and the "quality management system" approach- a system widely adopted internationally. Development of a quality management system is likely to play an important role in the ability of labs to receive test referrals from international sources, as well as improving their quality management.

Highlights: Laboratories should publicize which genetic tests they offer to all potential users, including clinicians and patients. This may include print and electronic media. Laboratories should also include information to guide decision making about the test itself. Such data should include the following: The recommended patient populations for testing, Test method used, The reliability of the test, Whether the test is performed with approved test system, Limitations of the test, A statement that the result may likely have implications for the family. Information regarding the cost of testing should also be included, if possible. Informed consent should remain the responsibility of the person ordering the genetic test. However, laboratories may aid in the process of shared decision making by being available to answer questions during the consent process and using test order forms that acknowledge that patient consent was obtained before the test was ordered. Obtaining information on indications for testing, relevant clinical or laboratory information, patient racial/ethnic background, family history, and pedigree is critical for selecting appropriate test methods, determining the mutations or variants to be tested, interpreting test results, and reporting test results in a timely manner. Laboratories are required to establish analytic performance specifications and then establish quality-control procedures to ensure that these specifications are met consistently. This can be a particular challenge with molecular genetic testing in patients with diverse backgrounds. Performance assessment for each type of molecular genetic test offered should be performed at least twice annually. Formal proficiency testing is available for a limited number of genetic tests and is preferred. Reports from molecular genetic testing should be kept on file at the laboratory for at least 25 years after reporting. Maintenance of patient confidentiality is critically important with regard to results from genetic testing. Laboratories may release patient test information only to the authorized person ordering the test, healthcare providers authorized by the ordering person to receive the test, and the laboratory that initially requested the test. If a healthcare provider who provides care for a family member of the patient is authorized to request patient test information, the laboratory should request the patient's authorization before releasing the patient's genetic test results.

TULIP NEWS

Feel, the SILENT CRY,

of Kidneys...



Introducing

Quantia
Cystatin C
Responsive Marker of GFR

Quantia Cystatin C - BENEFITS

- **High specificity** due to use of latex coated with purified immunoglobulin fraction directed against Cystatin C
- **High sensitivity** and reagent stability due to covalent binding of Anti Cystatin C to latex particles
- **No interference** from Rheumatoid factor due to use of avian antibodies
- **Accuracy** due to Traceability to coming IFCC/EU International Standard for Cystatin C
- **Versatile** as it can be adapted on most chemistry analyzers

Cystatin C - Meets requirements of Ideal GFR marker

- Non-glycosylated gamma trace protein **produced at a constant rate** by the nucleated cells
- Low molecular weight protein **freely filtered from glomerulus**
- Reabsorbed but almost **completely catabolized in the proximal renal tubule**
- **Not secreted** by renal tubules
- Virtually **constant reference values** in healthy individuals
- **Not influenced by age, muscle mass,** infections, liver diseases, or inflammatory diseases

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