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Summary of European recommendations on nephrology

Study guide

Edited by doctor of medical sciences, professor L. N. Prystupa

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The study guide is recommended for students of 5–6 courses in the discipline of «Internal Medicine», as well as for interns in the specialties of "Internal Diseases" and "General Practice – Family Medicine".

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INTRODUCTION

The summary of the European recommendations on nephrology contains questions of etiology, pathogenesis, classification, diagnostics and modern methods of treatment from the standpoint of modern medicine and in accordance with the latest European clinical guidelines. The requirements of the modern international nomenclature are observed.

The study guide can be recommended for 4^{th}–6^{th} year students in the discipline of Internal Medicine, as well as for interns in the specialties of Internal Medicine and General Practice – Family Medicine.

RENAL FUNCTION AND STRUCTURE

KIDNEY FUNCTION

The function of the kidney is to maintain the internal environment (internal milieu) of the body stable within the physiological limits. This is achieved through the following functions:

1 EXCRETORY FUNCTION AND PRODUCTION OF URINE

The production of urine from blood perfusing the kidney occurs in two steps: the first is the filtration of plasma in the glomeruli; and the second is the selective reabsorption or excretion of various substances in the renal tubules. Through urine excretion there is (1) removal of waste products (metabolic products, ingested toxins such as drugs); (2) control of water balance (maintenance of total body water and plasma osmolarity); and (3) control of electrolyte balance (sodium, chloride, calcium, phosphate, potassium, acid base, magnesium and others).

2 REGULATION OF ACID-BASE BALANCE OF THE BODY

When excess acids are released into the circulation (e. g. through metabolic process, acid intake, or respiratory failure), the kidney prevents acidosis (accumulation of H+ and drop in pH) through different mechanisms such as:

a) Excessive proximal tubular reabsorption of bicarbonate filtered from blood through the glomeruli. This reabsorbed bicarbonate will go through the blood and acts as a buffer to neutralize excess H+ in the circulation ($H^+ + HCO_3 \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$);

b) Excessive consumption and excretion of H+ by the renal tubules through the increase in the formation of ammonia and titratable acids (phosphates, sulphates and phenols).

In case of alkalosis (low H+ concentration pH of body fluids), the kidney will compensate by increasing bicarbonate loss in urine. This compensation occurs by increasing its reabsorption which will then lead to increase of H^+ in the blood through the reaction $H_2CO_3 \rightarrow H^+ + HCO_3–$. Also formation of ammonia and secretion of titratable acids by renal tubules will decrease. This results in retention of H^+ in blood and tissue fluids with correction of alkalosis. In states of acidosis, a patient with normal kidney will have maximum acidic urine (less than 5.5) and in state of alkalosis the urine will be alkalotic.

3 HEMOPOIETIC FUNCTION

Kidney has an important role in erythropioesis in the bone marrow through secretion of erythropoietin.

Erythropoietin is a hormone of glycoprotein nature which regulates red blood cell development in the bone marrow. Ninety percent of erythropoietin is produced in renal cortex (by interstitial, tubular or endothelial cells). The main stimulus for erythropoietin secretion is tissue hypoxia; other stimuli are androgens, PGE, thyroid hormone and B-adrenergic agonists. Inability to secrete sufficient amount of erythropoietin as in chronic renal failure results in anemia. In contrary, in conditions such as renal artery stenosis, cystic kidney diseases, and renal cell carcinoma, erythropoietin is secreted in excess, resulting in polycythaemia (Erythrocytosis). Human recombinant erythropoietin is now commercially available for the treatment of anemia in uremic patients.

4 ENDOCRINE FUNCTIONS OF THE KIDNEY

Many hormones and vasoactive substances are either formed, activated, or degraded by the kidney. Examples of these functions are listed below.

Hormones Synthesized by the Kidneys

Renin is secreted by cells of the iuxta-glomerular apparatus. Renin will act on a circulating protein (angiotensinogen) changing it to angiotensin I, which is then converted by the enzyme to angiotensin II, which has vasopressor activity, and also stimulates suprarenal gland to secrete aldosterone. This system (renin-angiotensin-aldosterone) is of great importance for controlling blood pressure and body fluid and electrolyte balance.

Activation of vitamin D: Vitamin D reaching the body through oral intake or formed subcutaneously (by exposure to sun or ultraviolet rays) is biologically inactive. The activation of this vitamin occurs through hydroxylation (OH). The first step of hydroxylation occurs in the liver (25-OH-vitamin D), whereas the second step occurs in the kidney (1,25-(OH)2 Vitamin D). The 1,25-dihydroxy vitamin D is 100 times as active as 25-hydroxy vitamin D. Parathormone and hypophosphataemia are the main stimuli for renal production of 1,25-(OH)2 vit. D. The exact site of synthesis is unknown, although the 1-hydroxylase enzyme is found in proximal tubular cells. The major effects of vitamin D are to increase gastrointestinal calcium absorption and to promote normal bone calcification. Also vitamin D and its metabolites have important effects on skeletal muscle strength.

Prostanoids (Prostaglandins) are derived from oxidation of arachidonic acid and other polyunsaturated fatty acids and have great diversity of structure and biological

effects. They are not strictly hormones since they act in the organ in which they are produced. The term “autacoids” has been introduced to describe such locally acting agents. The kidney has enzymes to produce all known primary prostanoids, and appears to be able to adapt this process according to various circumstances.

Prostanoids may be divided into those with vasodilator, diuretic and antithrombotic effects (prostacyclin, PGE2, PGD2), and those with opposing actions (thromboxane).

Kallikrein-Bradykinin are vasodilator autacoids found particularly in renal cortex. Effects of kallikrein-kinin include (1) decreased renal vascular resistance, particularly in low sodium states; (2) augment renal sodium and water excretion; and (3) activation of prostaglandin synthesis and apparantly a role in complex relationships with other regulatory substances.

Peptide Hormones Degraded by the Kidneys

The kidney removes many peptide hormones from circulation to be degraded by renal tubules. This removal can occur through reabsorption from the glomerular filtrate (from within) or by peptide to the specific receptors on the basolateral tubular cell membrane.

Insulin: Nearly 25 % of insulin, pro-insulin and c-peptide are removed from the circulation by the two previously described mechanisms. For example, in diabetics, the need for insulin is often reduced in end-stage renal failure. On the other hand, uraemia can cause peripheral insulin resistance with consequent carbohydrate intolerance.

Parathormone (PTH): About 30 % of the total metabolism of PTH occurs in the renal tubules. The intact hormone, c-terminal and amino-terminal are removed through glomerular filtration, while intact hormone and amino-terminal are removed from the peritubular circulation by binding to

specific receptors. Elevated plasma PTH in uraemia is partly due to impaired renal metabolism.

Prolactin: Prolactin metabolism mainly occurs through the renal (glomerular filtration) mechanism. Elevated prolactin levels are observed in 60 % of uremic patients indicating a disruption of pituitary gland feedback. This may be the cause of gynaecomastia, galactorrhea, infertility and impotence in chronic renal failure.

Growth hormone: The kidney removes 40-70 % of growth hormone from circulation (glomerular filtration).

Vasopressin: The kidney removes 30-50 % of this hormone through glomerular filtration.

Glucagon: About 30 % of this hypoglycaemic hormone is renally excreted.

Gastrointestinal hormones: Gastrin, VIP, and gastric inhibitory polypeptide are all partially excreted by the kidneys.

Hormones Acting on the Kidneys

Antidiuretic hormone (AHD)(vasopressin): ADH is produced by the cells of the supraoptic nucleus of the hypothalamus and is released from the posterior pituitary.

The main effects of ADH are (1) to increase the permeability of the collecting tubules for water, allowing it to flow back into the circulation. This leads to urine concentration and water retention; and (2) it causes vasoconstriction, which leads to an increase in blood pressure.

Stimuli to secretion of ADH include: (1) Decrease in effective blood volume, which triggers pressure sensors in cardiac atria, aortic arch and carotid sinuses. The response curve is exponential. Therefore, the volume stimuli override osmolar stimuli. By this mechanism decreased effective blood volume, such as in cirrhosis and cardiac failure, results in excess secretion of ADH with water retention irrespective of the developing hyponatremia (dilution) and hypo-osmolarity.

(2) Increase in plasma osmolarity. Sensitive osmoreceptors exist in the hypothalamus, and the response is linear. Sodium chloride is a powerful stimulant for secretion of ADH, while urea, glucose and ethanol are very weak stimulants. (3) Many other stimuli, including nausea, hypoglycemia, high ambient temperature, anxiety and stress are also associated with release of ADH.

Synthetic analogues of ADH include (1) 8-arginine vasopressin-AVP, which is available for parenteral or intranasal use for ADH deficiency; and (2) Desamino-D-arginine vasopressin (DDAVP) is a synthetic analogue whith increased antidiuretic but decreased vasoconstrictor action compared with AVP.

Atrial natriuretic peptide (ANP): ANP is a 28-amino acid peptide which is released from granules in the cardiac atria in response to stretch. ANP has renal (diuretic and natriuretic) and hemodynamic (hypotensive) actions. It also has important hormonal actions such as suppression of renin and aldosterone.

Mineralocorticoids and glucocorticoids: Aldosterone is a steroid hormone produced by the adrenal cortex in response to adrenocorticotrophic hormone, hyperkalaemia or angiotensin II. Its main action extends to the late distal tubule and early collecting duct. It reduces excretion of sodium and, consequently, increases excretion of potassium. Aldosterone excess can occur as a primary phenomenon (Conn's Syndrome) or more commonly secondary to an excess of rennin, as in oedema, renal artery stenosis, and with malignant hypertension. Glucocorticoids at high doses have mineralocorticoid effects.

Dopamine is released by the renal nerves, probably secondary to baroreceptors stimulation. It causes renal vasodilatation and natriuresis mainly through stimulation of kallikrein-kinin system. It may be used in some cases of acute renal failure to maintain renal perfusion and urine output.

BLOOD SUPPLY OF THE KIDNEY

The *renal arteries* arise from the aorta opposite the intervertebral disc L 1-2. In the hilum, it gives anterior and posterior branches, which, penetrating into kidney tissue, form *interlobar arteries*, running between the renal pyramids. At corticomedullary junction, they turn to run along the base of the pyramids, forming the arcuate arteries and at 90° exit *interlobular arteries*, which penetrate into the cortex and from them depart the *afferent arterioles*. At the glomerulus, afferent arteriole invaginates the Bowman's capsule, forming the glomerular tuft, which is a modified capillaries structure from which glomerular filtrate exits into the urinary space of the Bowman's capsule. The efferent arteriole emerges from the glomerulus. The efferent arterioles of the outer and middle cortical glomeruli descend between the tubules, where they divide into capillary networks called peritubular capillaries. The efferent arterioles of the inner cortical glomeruli penetrate deeply into the medullary pyramids, forming *vasa recta,* which participate in the system of medullary counterflow exchange. The vasa recta vessels dive deeply into the medullary pyramids, then make a hairpin turn, returning to the corticomedullary junction. Note that

- The renal venous system follows the same pattern as the renal arteries.
- The lymphatic vessels run in conjunction with the blood vessels.
- The kidney receives sympathetic and parasympathetic fibers from the celiac plexus.

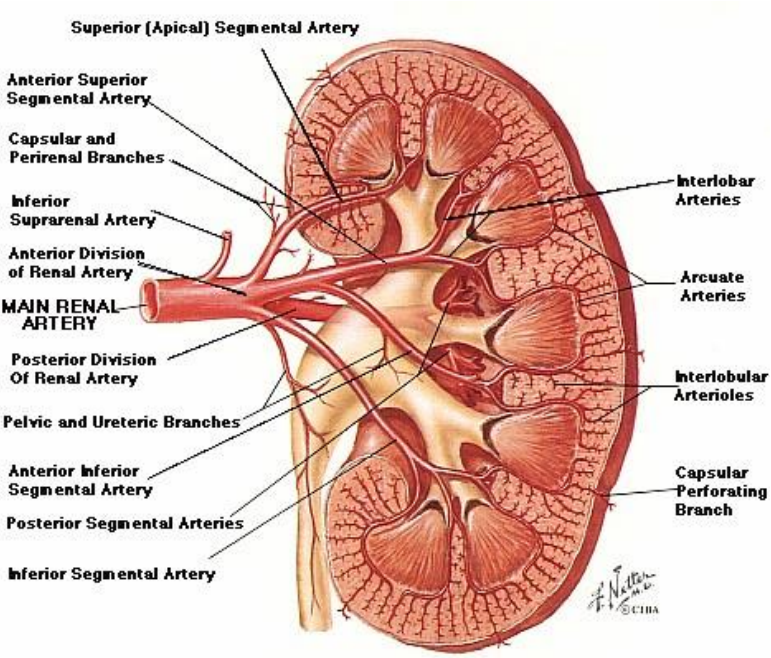

Figure 1 - Terminal branches of the renal artery (left kidney viewed from the front)

GLOMERULONEPHRITIS

Introduction

Two human kidneys harbor nearly 1.8 million glomerular capillary tufts. Each glomerular tuft resides within Bowman's space. The capsule circumscribing this space is lined by parietal epithelial cells, which transition into tubular epithelia that form the proximal nephron. The glomerular capillary tuft derives from the afferent arteriole, which forms a branching capillary bed embedded in mesangial matrix. This capillary network flows into the efferent arteriole, which

conveys filtered blood to the cortical peritubular capillaries or medullary vasa recta, which supply and exchange with the folded tubular architecture. Hence the glomerular-capillary tuft, fed and drained by arterioles, is an arteriolar portal system. Fenestrated endothelial cells, resting on a glomerular basement membrane (GBM), line glomerular capillaries. Delicate foot processes, extending from epithelial podocytes, shroud the outer surface of these capillaries, and podocytes are connected to each other by slit-like pore membranes, forming a selective filtration barrier.

The glomerular capillaries filter 120–180 L/d of plasma water containing various solutes for reclamation or excretion by downstream tubules. Most large proteins and all cells are excluded from filtration by a physicochemical barrier governed by pore size and negative electrostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes. For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albumin has a negative charge, which would tend to repel the negatively charged GBM, it has a physical radius of 3.6 nm, while pores in the GBM and slit-pore membranes have a radius of 4 nm. Consequently, considerable amounts of albumin (estimates range from 4000 to 9000 mg/d) inevitably cross the filtration barrier to be reclaimed by megalin and cubilin receptors along the proximal tubule. It is remarkable that humans with normal nephrons excrete no more than 8–10 mg of albumin in their daily urine. This amount of albumin, and other proteins, can rise to gram quantities following glomerular injury.

The spectrum of diseases affecting the glomeruli is vast, as the glomerular capillaries can be injured in many different ways, causing many different lesions and unique changes in the urinalysis. Some order to this vast subject is brought by grouping all of these diseases into a smaller number of clinical syndromes.

Pathogenesis of Glomerular Disease

There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called *idiopathic*. Specific or unique features of pathogenesis are mentioned when describing each of the glomerular diseases.

Some glomerular diseases result from genetic mutations, producing familial disease:

1 Congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations in adulthood produce *focal segmental glomerulosclerosis* (FSGS).

2 Partial lipodystrophy from mutations in genes, encoding lamin A/C or PPAR, cause a metabolic syndrome that can be associated with *membranoproliferative glomerulonephritis* (MPGN), which is sometimes accompanied by dense deposits and C3 nephritic factor.

3 Alport's syndrome, from mutations in the genes encoding for the 3-, 4-, or 5-chains of type IV collagen, produces *split-basement membranes* with *glomerulosclerosis*.

4 Lyposomal storage disease, such as galactosidase A deficiency, causing Fabry's disease, and *N*-acetylneuraminic acid hydrolase deficiency, causing nephrosialidosis, produce FSGS.

Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to *chronic glomerulosclerosis. Malignant hypertension* can quickly complicate glomerulosclerosis with fibrinoid necrosis of arterioles and glomeruli, thrombotic microangiopathy, and

acute renal failure. *Diabetic nephropathy* is an acquired sclerotic injury associated with thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end-products, and reactive oxygen species.

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are antigens. Glomerular epithelial or mesangial cells can shed them or express epitopes that mimic other immunogenic proteins produced elsewhere in the body. Bacteria, fungi, and viruses can directly infect the kidney, producing their own antigens. Autoimmune diseases, like idiopathic *membranous glomerulonephritis* (MGN) or MPGN, are confined to the kidney, while systemic inflammatory diseases, like *lupus nephritis* or *Wegener's granulomatosis,* spread to the kidney, causing secondary glomerular damage. *Antiglomerular basement membrane disease* producing Goodpasture's syndrome primarily injures both the lung and kidney, because of the narrow distribution of the 3 NC1 domain of type IV collagen that is the target antigen.

While the adaptive immune response is similar to that of other tissues, early T cell activation plays an important role in the mechanism of glomerulonephritis. Antigens presented by class II major histocompatibility complex (MHC) molecules on macrophages and dendritic cells in conjunction with associative recognition molecules engage the CD4/8 T cell repertoire. Local activation of Toll-like receptors on glomerular cells, deposition of immune complexes, or complement injury to glomerular structures induces mononuclear cell infiltration, which subsequently leads to an adaptive immune response attracted to the kidney by local release of chemokines. Neutrophils, macrophages, and T cells are drawn by chemokines into the glomerular tuft, where they react with antigens and

epitopes on or near somatic cells or their structures, producing more cytokines and proteases that damage the mesangium, capillaries, and/or the GBM.

Mononuclear cells can damage the kidney on their own, but autoimmune events that damage the glomeruli classically trigger a humoral immune response. *Poststreptococcal glomerulonephritis*, *lupus nephritis*, and idiopathic *membranous nephritis* typically are associated with immune deposits along the GBM, while anti-GBM antibodies are produced in anti-GBM disease. Pre-formed circulating immune complexes can be deposited on the subendothelial side of the GBM, while other immune deposits are formed in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigen-antibody interactions. Immune deposits can stimulate the release of local proteases and activate the complement cascade, producing $C_{5\text{-}9}$ attack complexes. In addition, local oxidants can damage glomerular structures, сфгыштп proteinuria and effacement of the podocytes. Overlapping etiologies or pathophysiologic mechanisms can produce similar glomerular lesions, suggesting that downstream molecular and cellular responses often converge towards common patterns of injury.

Progression of Glomerular Disease

Persistent glomerulonephritis that worsens renal function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy. What is not so obvious, however, is that renal failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury.

Loss of renal function due to interstitial damage can be explained hypothetically by several mechanisms. The simplest explanation is that urine flow is impeded by tubular obstruction as a result of interstitial inflammation and fibrosis. Thus, obstruction of the tubules with debris or by extrinsic compression results in aglomerular nephrons. The second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture and thereby compromise the normal tubular transport of solutes and water from tubular lumen to vascular space. This failure increases the solute and water content of the tubule fluid, resulting in isothenuria and polyuria. Adaptive mechanisms related to tubuloglomerular feedback also fail, resulting in a reduction of renin output from the juxtaglomerular apparatus of glomeruli trapped by interstitial inflammation. Consequently, the local vasoconstrictive influence of angiotensin II on the glomerular arterioles decreases, and filtration drops due to a general decrease in arteriolar tone. The third mechanism involves changes in vascular resistance due to damage of peritubular capillaries. The cross-sectional volume of these capillaries decreases in the areas of interstitial inflammation, edema, or fibrosis. These structural alterations in vascular resistance affect renal function through two mechanisms. First, tubular cells are very metabolically active, and, as a consequence, reduce perfusion can lead to ischemic injury. Second, impairment of glomerular arteriolar outflow leads to increased intraglomerular hypertension in the less involved glomeruli; this selective intraglomerular hypertension aggravates and expands *mesangial sclerosis* and *glomerulosclerosis* in the less-involved glomeruli. Regardless of the exact mechanism, early *acute tubulointerstitial nephritis* suggests potentially recoverable renal function, while the development of *chronic interstitial fibrosis* prognosticates a permanent loss.

Persistent damage to glomerular capillaries spreads to tubulointerstitium due to proteinuria. There is an untested hypothesis that efferent arterioles leading from inflamed glomeruli carry forward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glomerular capillaries adherent to Bowman's capsule may also be misdirected to the periglomerular interstitium. Most nephrologists believe, however, that proteinuric glomerular filtrate forming tubular fluid is the primary route to downstream tubulointerstitial injury, although none of these hypotheses are mutually exclusive.

The simplest explanation for the effect of proteinuria on the development of interstitial nephritis is that increasingly severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells lining the tubular nephron. These effects induce T lymphocyte and macrophage infiltrates in the interstitial spaces along with fibrosis and tubular atrophy.

Tubules disappear following direct damage to their basement membranes, leading to decondensation and epithelial-mesenchymal transitions, forming more interstitial fibroblasts at the injury site. Transforming growth factor (TGF), fibroblast grow factor 2, and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagens I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hematopoietic growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, they apoptose, and the permanent renal scar becomes acellular, leading to irreversible renal failure.

Hematuria, Proteinuria, and Pyuria

Patients with glomerular disease usually have some hematuria with varying degrees of proteinuria. Hematuria is typically asymptomatic. As little as 3–5 red blood cells in the spun sediment from first voided morning urine is suspicious. The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria*, and only rarely with the exception of IgA nephropathy and sickle cell disease is *gross hematuria* present. When working up microscopic hematuria, perhaps accompanied by minimal proteinuria (<500 mg/24 h), it is important to exclude anatomic lesions, such as malignancy of the urinary tract, particularly in older men. Microscopic hematuria may also appear with the onset of benign prostatic hypertrophy, interstitial nephritis, papillary necrosis, renal stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts or dysmorphic red blood cells are found in the sediment, glomerulonephritis is likely.

Sustained proteinuria >1–2 g/24 h is also commonly associated with glomerular disease. Patients often will not know they have proteinuria unless they become edematous or notice foamy urine on voiding. *Sustained proteinuria* has to be distinguished from lesser amounts of so-called *benign proteinuria* in the normal. This latter class of proteinuria is nonsustained, generally <1 g/24 h, and is sometimes called *functional* or *transient proteinuria.* Fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure can explain transient proteinuria. Proteinuria only seen with upright posture is called *orthostatic proteinuria.* Occasionally, isolated proteinuria sustained over multiple clinic visits is found in diabetic nephropathy, *nil lesion, mesangioproliferative glomerulonephritis*, and FSGS. Proteinuria in most adults with glomerular disease is *nonselective*, containing albumin and a mixture of other serum proteins, while in children with nil

lesion from *minimal change disease*, the proteinuria is *selective* and largely composed of albumin.

Some patients with inflammatory glomerular disease, such as acute poststreptococcal glomerulonephritis or MPGN, may have *pyuria* caused by the presence of considerable numbers of leukocytes in the urine. This latter finding has to be distinguished from urine infected with bacteria.

Clinical Syndromes

Various forms of glomerular injury can also be parsed into several distinct syndromes on clinical grounds. These syndromes, however, are not always mutually exclusive. There is an *acute nephritic syndrome* producing 1–2 g/24 h of proteinuria, hematuria with red blood cell casts, pyuria, hypertension, fluid retention, and a rise in serum creatinine associated with a reduction in glomerular filtration. If glomerular inflammation develops slowly, the serum creatinine will rise gradually over many weeks, but if the serum creatinine rises quickly, particularly over a few days, acute nephritis is sometimes called *rapidly progressive glomerulonephritis* (RPGN); the histopathologic term *crescentic glomerulonephritis* refers to the clinical occurrence of RPGN in a patient with this characteristic glomerular lesion. When patients with RPGN present with lung hemorrhage from Goodpasture's syndrome, antineutrophil cytoplasmic antibodies (ANCA) small-vessel vasculitis, lupus erythematosus, or cryoglobulinemia, they are often diagnosed as having a *pulmonary-renal syndrome. Nephrotic syndrome* describes the onset of heavy proteinuria (>3.0 g/24 h), hypertension, hypercholesterolemia, hypoalbuminemia, edema/anasarca, and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations, the condition is sometimes called *nephrotic-range proteinuria*. The glomerular filtration rate (GFR) in these patients may initially be normal

or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes or an autoimmune response to basement membrane collagen IV associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine. *Glomerular-vascular syndrome* describes patients with vascular injury producing hematuria and moderate proteinuria. Affected individuals can have vasculitis, thrombotic microangiopathy, antiphospholipid syndrome, or, more commonly, a systemic disease such as atherosclerosis, cholesterol emboli, hypertension, sickle cell anemia, and autoimmunity. *Infectious diseases-associated syndrome* is most important if one has an international perspective. Save for subacute bacterial endocarditis in the Western Hemisphere, malaria and schistosomiasis may be the most common causes of glomerulonephritis throughout the world, closely followed by HIV and chronic hepatitis B and C. These infectious diseases produce a variety of inflammatory reactions in glomerular capillaries, ranging from nephrotic syndrome to acute nephritic injury, and yield urinalyses that demonstrate a combination of hematuria and proteinuria.

Table 1

Glomerular Syndromes	**Proteinuria**	**Hematuria**	**Vascular Injury**
Acute Nephritic Syndromes			
Subacute bacterial endocarditis[a]	+/++	++	–
Lupus nephritis[a]	+/++	++/+++	–
Lupus nephritis[a]	+/++	++/+++	–
Antiglomerular basement membrane disease[a]	++	++/+++	–
IgA nephropathy[a]	+/++	++/+++[c]	–

Continuation of Table 1

Glomerular Syndromes	**Proteinuria**	**Hematuria**	**Vascular Injury**
ANCA small-vessel vasculitis[a]			
Wegener's granulomatosis	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Membranoproliferative glomerulonephritis[a]	++	++/+++	–
Mesangioproliferative glomerulonephritis	+	+/++	–
Pulmonary-Renal Syndromes			
Goodpasture's syndrome[a]	++	++/+++	–
ANCA small-vessel vasculitis[a]			
Wegener's granulomatosis	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	–	–
Focal segmental glomerulosclerosis	+++/++++	+	–
Membranous glomerulonephritis	++++	+	–
Diabetic nephropathy	++/++++	–/+	–
AL and AA amyloidosis	+++/++++	+	+/++
Light-chain deposition disease	+++	+	–
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry's disease	+	+	–
Basement Membrane Syndromes			
Anti-GBM disease[a]	++	++/+++	–
Alport's syndrome	++	++	–
Thin basement membrane disease	+	++	–
Nail patella syndrome	++/+++	++	–

Continuation of Table 1

Glomerular Syndromes	**Proteinuria**	**Hematuria**	**Vascular Injury**
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy[b]	+/++	+/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	++	+++
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis[a]			
Wegener's granulomatosis	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++
Infectious Disease-Associated Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
HIV	+++	+/++	–
Hepatitis B and C	+++	+/++	–
Syphilis	+++	+	–
Leprosy	+++	+	–
Malaria	+++	+/++	–
Schistosomiasis	+++	+/++	–
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–

Note: *[a] Can manifest as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis.*

[b] Can manifest as a malignant hypertensive crisis, producing an aggressive fibrinoid necrosis in the arterioles of small arteries with microangiopathic hemolytic anemia.

[c] Can manifest with gross hematuria.

Abbreviations: *ANCA - antineutrophil cytoplasmic antibodies; AL - amyloid L; AA - amyloid A; GBM - glomerular basement membrane.*

These six general categories of syndromes are usually determined at the bedside with the help of a history and physical examination, blood chemistries, renal ultrasound, and urinalysis. These initial studies help frame further diagnostic work up that typically involves some testing of the serum for the presence of various proteins (HIV and hepatitis B and C antigens), antibodies [anti-GBM, antiphospholipid, ASO, anti-DNAase, antihyaluronidase, ANCA, anti-DNA, cryoglobulins, anti-HIV, and anti-hepatitis B and C antibodies] or depletion of complement components (C_3 and C_4). The bedside history and physical examination can also help determine whether the glomerulonephritis is isolated to the kidney (*primary glomerulonephritis*) or is part of a systemic disease (*secondary glomerulonephritis*). When confronted with an abnormal urinalysis and elevated serum creatinine, with or without edema or congestive heart failure, one must consider whether the glomerulonephritis is *acute* or *chronic*. This assessment is best made by careful history (last known urinalysis or serum creatinine during pregnancy or insurance physical, evidence of infection, or use of medication or recreational drugs); the size of the kidneys on renal ultrasound examination; and how the patient feels at presentation. Chronic glomerular disease often presents with decreased kidney size. Patients who quickly develop renal failure are fatigued and weak; feel miserable; often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence. Primary glomerulonephritis presenting with renal failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis without much loss in renal function. Once this initial information is collected, selected patients who are clinically stable, have adequate blood clotting parameters,

and are willing to receive treatment are encouraged to have a renal biopsy. Biopsies can be done safely with an ultrasound-guided biopsy gun.

Renal Pathology

A renal biopsy in the setting of glomerulonephritis can quickly identify the type of glomerular injury and often suggests a course of treatment. The biopsy is processed for light microscopy using stains for *hematoxylin and eosin* (H&E) to assess cellularity and architecture, *periodic acid-Schiff* (PAS) to stain carbohydrate moieties in the membranes of the glomerular tuft and tubules, *Jones-methenamine silver* to enhance basement membrane structure, *Congo red* for amyloid deposits, and *Masson's trichrome* to identify collagen deposition and assess the degree of glomerulosclerosis and interstitial fibrosis. Biopsies are also processed for direct immunofluorescence using conjugated antibodies against IgG, IgM, and IgA to detect the presence of "lumpy-bumpy" immune deposits or "linear" IgG or IgA antibodies bound to GBM, antibodies against trapped complement proteins (C_3 and C_4), or specific antibodies against a relevant antigen. High-resolution electron microscopy can clarify the principal location of immune deposits and the status of the basement membrane.

Each region of a renal biopsy is assessed separately. By light microscopy, glomeruli (at least 10 and ideally 20) are reviewed individually for discrete lesions; <50% involvement is considered *focal*, and >50% is *diffuse*. Injury in each glomerular tuft can be *segmental*, involving a portion of the tuft, or *global*, involving most of the glomerulus. Glomeruli can have *proliferative* characteristics, showing increased cellularity. When cells in the capillary tuft proliferate, it is called *endocapillary*, and when cellular proliferation extends into Bowman's space, it is called *extracapillary*. *Synechiae* are

formed when epithelial podocytes attach to Bowman's capsule in the setting of glomerular injury; *crescents*, which in some cases may be the extension of synechiae, develop when fibrocellular/fibrin collections fill all or part of Bowman's space; and *sclerotic* glomeruli show acellular, amorphous accumulations of proteinaceous material throughout the tuft with loss of functional capillaries and normal mesangium. Since *age-related glomerulosclerosis* is common in adults, one can estimate the background percentage of sclerosis by dividing the patient's age in half and subtracting 10. Immunofluorescent and electron microscopy can detect the presence and location of *subepithelial, subendothelial, or mesangial* immune deposits, or *reduplication* or *splitting* of the basement membrane. In the other regions of the biopsy, the vasculature surrounding glomeruli and tubules can show *angiopathy, vasculitis*, the presence of *fibrils*, or *thrombi*. The tubules can be assessed for adjacency to one another; separation can be the result of edema, tubular dropout, or collagen deposition resulting from interstitial fibrosis. Interstitial fibrosis is an ominous sign of irreversibility and progression to renal failure.

Acute nephritic syndromes classically present with hypertension, hematuria, red blood cell casts, pyuria, and mild to moderate proteinuria. Extensive inflammatory damage to glomeruli can cause a fall in GFR and eventually produce uremic symptoms with salt and water retention, leading to edema and hypertension.

Poststreptococcal Glomerulonephritis

Poststreptococcal Glomerulonephritis (PSGN) is characterized by the abrupt onset of hematuria and proteinuria, often in association with edema, hypertension, and mild/moderate renal insufficiency. The disease usually develops several days after a pharyngeal or cutaneous infection

caused by group A beta-hemolytic streptococci. The prognosis of PSGN is usually good in the short and long term, but some patients have excessive salt and water retention, and others may slowly progress to renal failure.

Etiology and Epidemiology

PSGN is associated with infections caused by a limited number of strains of group A beta-hemolytic streptococci. These nephritogenic streptococci may be identified by serotyping of a cell wall antigen calledMprotein. In most cases, streptococcal infection occurs in the upper respiratory tract or in the skin.

Less commonly, PSGN may be preceded by otitis or endocarditis, and may be triggered by other streptococci such as *Streptococcus viridans, Streptococcus mitis* or *Streptococcus mutans*. It must be remembered that in several cases acute GN is not caused by streptococci but is associated with a bacteremic state or with viral or parasitic diseases.PSGN is the most common primary GN in developing countries, while in the Western world it has become an uncommon disease, suggesting that it is favored by low socioeconomic status and poor hygienic conditions.

This is also confirmed by the cases occurring in clusters and epidemics, which at times may be even cyclic. All ages can be affected by PSGN. However, most patients are between 2 and 12 years old. PGN is twice as common in males as in females.

Pathology

In the early phases, there is diffuse mesangial and endothelial cell proliferation, associated with infiltration of the capillary lumens by polymorphonuclear leukocytes and mononucleated cells. Extracapillary proliferation may involve

a few glomeruli, while diffuse and extensive circumferential crescent formation is uncommon, although possible. Cells expressing interleukin-8 (IL-8) and transforming growth factor-beta (TGF/) [125], as well as cells with increased expression of intercellular adhesion molecule-1 (ICAM-1) can be found both in glomeruli and interstitium. IL-8 correlates with glomerular neutrophil infiltration, while TGF correlates with mesangial matrix expansion. The tubulointerstitial compartment is usually normal, but in the most proliferative forms acute cellular infiltrates can be seen. The typical immunohistologic pattern is characterized by abundant and well-defined granular deposits of C3 along the outer aspects of the glomerular capillary walls. These deposits confer the appearance known as “starry sky”. IgG and IgM are present in 60–70 % of cases. C1q and C4 are generally lacking. Fibrinogen is seen only in crescents. By electron microscopy, coarse electrondense subepithelial deposits are the distinguishing feature of PSGN. Due to their shape, the deposits are defined as humps. However, intramembranous and subendothelial deposits, as well as mesangial deposits, can also be found. In later phases of the disease, endocapillary proliferation and polymorphonuclear infiltration are less evident, and prominent mesangial deposits can be observed. In other cases, subepithelial deposits are confluent, so that the humps are replaced by apparently elongated deposits, which confer a garland-like pattern at immunohistology. In cases without complete resolution, the typical endocapillary disease can transform, over time, into a mesangiocapillary pattern.

Pathogenesis

Some data suggest that PSGN is an immune- complex disease, in which some components of nephritogenic streptococci are likely to act as antigens. Cell membrane antigens, streptococcal cationic proteinase, extracellular

plasmin-binding protein, and endostreptosin or preabsorbing antigen have been proposed as possible triggers for the formation of the immune complexes. On the other hand, anti-immunoglobulin antibodies could be involved in the pathogenesis of PSGN, as demonstrated by the high titers of rheumatoid factor and by the presence of antiimmunoglobulin deposits in the renal biopsy of some patients. An important role in conferring antigenicity to immunoglobulins can be played by another streptococcal component, the neuraminidase. This, in fact, can cause desialization and consequent modifications of autologous immunoglobulins. Moreover, neuraminidase can desialize leukocytes and favor their deposition in the glomeruli and interstitium. Cellular immunity may also be involved in the pathogenesis of PSGN, as suggested by glomerular and interstitial infiltration of granulocytes, monocyte/macrophages, and T lymphocytes, increased IL-8 and TGF-ά in the kidneys, and increased IL-6 and tumor necrosis factor - (TNF-ά) in the circulation.

Clinical Presentation

The typical presentation of PSGN is an acute nephritic syndrome, i.e. oliguria, edema, hypertension, and gross hematuria 10–21 days after an upper respiratory tract or a skin infection. Nonspecific symptoms such as malaise, weakness, and nausea are frequent. Dull lumbar pain is present in 5–10 % of patients. Although rare, an extrarenal disease is possible in patients with PSGN, as demonstrated by the association with scleritis or cerebral vasculitis. Decreased GFR and salt and water retention are the main causes of edema and hypertension, as documented by the finding of increased plasma volume and cardiac output in most patients with PSGN. In children, edema is usually generalized, while in adolescents and adults it is more frequently confined to face and legs. Hypertension is observed in >80 % of patients, but in only 50 % of cases

require treatment. In rare cases, however, hypertension may be severe and cause hypertensive encephalopathy. Especially in elderly patients, oliguria and fluid retention can cause heart failure and death. Proteinuria is common in PSGN; however, nephrotic proteinuria is rare, especially in children. In other patients, PSGN can be asymptomatic and cause only transient serum complement decrease and/or mild urinary abnormalities such as isolated microscopic hematuria, with or without hypertension. Prospective studies in families have shown that this presentation is more frequent than the overt clinical presentation described above. Very rarely PSGN is not associated with urinary abnormalities in spite of clinical symptoms and the presence of endocapillary glomerulonephritis at biopsy. Usually, the nephritic symptoms spontaneously reverse 4–7 days after the onset. However, urinary changes, mild renal function impairment, or hypertension can persist or develop months or years after the acute episode. These abnormalities can be found in approximately 20 % of patients 1–2 decades after the onset. Usually children do better than adults. Patients with a nephrotic syndrome at presentation and those with extensive deposits in the peripheral capillary loops have a poorer prognosis. Patients with crescentic disease may recover spontaneously. However, the prognosis is poor when crescents involve >60 % of glomeruli. In some patients with subclinical presentation, persistent or intermittent microscopic hematuria may be seen at long-term follow-up.

Diagnosis

Several renal and systemic diseases can present with an acute nephritic syndrome: IgA nephropathy (IgAN), mesangiocapillary glomerulonephritis, anti-GBM disease, SLE, cryoglobulinemia, HSP, and systemic microscopic vasculitis. However, the finding of a preceding infection of the upper

respiratory tract or of the skin, increased antistreptolysin (ASO) titers, decreased C3 levels, and the lack or rareness of extrarenal symptoms strongly suggest a diagnosis of PSGN. In PSGN the infection typically precedes the nephritis by 10–21 days, while the episodes of gross hematuria in IgA nephropathy usually follow infections by hours or only a few days. In addition, while IgA nephropathy tends to cause repeated episodes of gross hematuria, PSGN is rarely recurrent. Increased ASO titers are observed in 40–90 % of patients with PSGN. This is much less common in other conditions. In PSGN, >90 % of patients have a decrease of C3 and normal C4 serum levels, indicating an activation of the alternative pathway of complement. In most cases C3 returns to normal in <8 weeks, even though a prolonged decrease of C3 is possible. The behavior of complement distinguishes PSGN from lupus nephritis in which both C3 and C4 are usually reduced in active phases. In type II cryoglobulinemic nephritis, usually only C4 is strongly decreased. In type IIMPGN, similar to PSGN, C3 is low while C4 is normal. However, C3 remains persistently low because of the presence of C3 nephritic factor. Usually, there are no extrarenal symptoms in PSGN besides edema and hypertension. This differentiates PSGN from systemic diseases causing acute nephritic syndrome. However, it should be remembered that in occasional patients with PSGN extrarenal symptoms such as scleritis and cerebral vasculitis may be present, and that even a positive ANCA is possible. PSGN can be easily diagnosed in epidemic or family cases, even when there are only transient and minor clinical and urinary changes. However, for sporadic cases with only persistent urinary abnormalities, distinguishing between IgA nephropathy, thin basement membrane disease, or other conditions can be difficult without renal biopsy. Is renal biopsy indicated for patients with acute nephritic syndrome caused by PSGN? For patients presenting with a typical history and clinical picture,

the diagnosis is easy and does not need a confirmatory biopsy. However, renal biopsy may be indicated for patients with atypical history or presentation, and especially for cases with severe or prolonged renal failure, which can be caused by crescentic disease.

Treatment

Patients with oliguria, edema, and hypertension need close observation and care. Restriction of sodium and fluid intake are mandatory. Furosemide or other loop diuretics are frequently needed. In many patients, hypertension reverses with the correction of fluid overload and edema. However, in some patients antihypertensive agents are needed. Antistreptococcal antibiotics such as penicillin, cephalosporins, erythromycin or derivatives should be given to patients with positive throat or skin cultures. Glucocorticoids or immunosuppressive agents are not indicated in PSGN because of spontaneous resolution of the disease in most cases. However, in patients with extensive crescent formation and slow resolution of symptoms, a short course of high-dose glucocorticoids may be considered.

The diagnosis of poststreptococcal GN requires the demonstration of antecedent streptococcal infection in a patient who presents with acute GN. Nephritis may follow 7–15 days after streptococcal tonsillitis and 4–6 weeks after impetigo. The nature of the nephritogenic streptococcal antigen is still controversial. Kidney biopsy is not indicated unless there are characteristics that make the diagnosis doubtful, or to assess prognosis and/or for potential therapeutic reasons. The kidney histology shows acute endocapillary GN with mesangial and capillary granular immune deposition. The clinical manifestations of acute nephritic syndrome usually last less than 2 weeks. Less than 4 % of children with poststreptococcal GN have massive proteinuria, and occasionally a patient

develops crescentic GN with rapidly progressive kidney dysfunction. Serum C3 values usually return to normal by 8–10 weeks after recognition of the infection. Persistent hypocomplementemia beyond 3 months may be an indication for a renal biopsy, if one has not already been performed. A lesion of MPGN is commonly found in persistently hypocomplementemic GN. The short-term prognosis of the acute phase of post- streptococcal GN is excellent in children; however, in elderly patients, mortality in some series is as high as 20 %. Although the long-term prognosis of poststreptococcal GN is debated, the incidence of ESRD in studies with 15 years of follow-up is less than 1 %, with the exception being that long-term prognosis is poor in elderly patients who develop persistent proteinuria. Well-documented streptococcal infection should be treated with penicillin, or erythromycin if the patient is allergic to penicillin, to resolve streptococcal infection and prevent the spread of the nephritogenic streptococcus among relatives or contacts. However, antibiotics are of little help for reversing GN, as the glomerular lesions induced by immune complexes are already established. The management of acute nephritic syndrome, mainly in adults, requires hospital admission if features of severe hypertension or congestive heart failure are present. Hypertension and edema usually subside after diuresis is established.

Adult patients persisting with urinary abnormalities beyond 6 months, especially if proteinuria 4.1 g/d, should receive ACE-I or ARBs as in other proteinuric glomerular diseases.

NEPHROTIC SYNDROME

Pathogenesis, Complications, and Treatment of the Nephrotic Syndrome

The term nephrotic syndrome refers to a clinical condition characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The nephrotic syndrome is often seen with urinary protein excretion >3.5 g/24 hours and is almost invariably present when proteinuria is >5 g/24 hours. The nephrotic condition may expose the patient to disabling and even life-threatening complications such as infections, bone disease, intravascular thrombosis, and cardiovascular disease. Moreover, the onset of the nephrotic syndrome is a marker for bad prognosis for most glomerular diseases.

Proteinuria

Proteinuria is a consequence of the disruption of the permeselectivity caused by the disease-related functional and/or anatomical damage of the glomerular basement membrane (GBM). Plasma proteins, particularly albumin, are allowed to pass through the glomerular capillary wall, exceeding the tubular reabsorptive capacity. There is now evidence that proteinuria may play a role in the progression of chronic renal failure (CRF). The abnormal filtration of proteins brings them into contact with the mesangium and with the proximal tubular cells. Mesangial accumulation of proteins may produce mesangial cell injury, mesangial cell proliferation, and increased production of mesangial matrix that eventually lead to glomerulosclerosis. The proximal reabsorption of proteins may trigger upregulation of inflammatory and vasoactive genes such as MCP-I and endothelins. The corresponding molecules formed in an excessive amount by renal tubuli are secreted toward the

basolateral compartment of the cell and give rise to an inflammatory reaction that leads to renal scarring.

Eradication of the underlying glomerular disease represents the best treatment for proteinuria. Some reduction of urinary protein excretion may also be obtained with diet and/or drugs. While a high-protein diet increases proteinuria, a low-protein diet may reduce urinary albumin excretion and increase serum albumin levels, at least in the short-term. ACE inhibitors can have an antiproteinuric effect, which is dose-dependent. The effect may require some weeks to be complete and is blunted by sodium intake. Angiotensin II (ANG II) receptor AT1 antagonists have a comparable antiproteinuric effect. ACE inhibitors may also slow the progression of chronic renal insufficiency. This beneficial effect may be independent of the blood pressure reduction and is particularly marked in patients with proteinuric glomerular diseases. Diet protein restriction, around 0.8 g per kg/day plus urinary losses, in combination with ACE inhibitors at the highest tolerated doses and restricted sodium intake may be recommended in patients with glomerular diseases to reduce urinary protein excretion and preserve renal function. It is possible but still unproven that the addition of AT1 receptor antagonist may further potentiate the antiproteinuric effect. Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce proteinuria by ≥50 % or more. The effect is rapid (within 1 week) and reverses after cessation of treatment. Indomethacin (150 mg/day) and meclofenamate (200–300 mg/day) are the 2 agents used most frequently. These agents can cause hyperkalemia, sodium retention, and acute renal failure (ARF) triggered by vasoconstriction or interstitial nephritis. Thus, careful monitoring of renal function is mandatory during treatment of nephrotic patients. The association with ACE inhibitors potentiates the antiproteinuric effect but increases the risk of renal function deterioration and hyperkalemia.

Hypoalbuminemia

Hypoalbuminemia plays a pivotal role in many complications of the nephrotic syndrome, including edema, malnutrition, hyperlipidemia, and cardiovascular disease. The urinary loss of albumin is not sufficient to explain hypoalbuminemia. There is also an increased catabolism of albumin that might contribute to hypoalbuminemia. However, the most important mechanism is the inability of the liver to increase the albumin synthesis in response to urinary losses and/or increased catabolism. Neither albumin infusion nor a high-protein diet may increase serum levels of albumin because these measures result in increased urinary losses of albumin.

Lipid Abnormalities

In nephrotic patients, there is an increase in low density lipoproteins (LDL), very low density lipoproteins (VLDL), and lipoprotein (a) (Lp(a)) levels while high density lipoprotein (HDL) levels are either normal or decreased. The composition of lipoproteins is also altered with a relative increase in cholesterol. These abnormalities are caused both by an increased hepatic synthesis and by a decreased clearance of lipids and lipoproteins. Experimental and clinical studies showed that cholesterol synthesis increased in response to hypoalbuminemia, serum cholesterol being inversely proportional to serum albumin. In addition to the increased synthesis, there are alterations in catabolism of lipids in nephrotic syndrome caused mainly by a decreased activity of the enzyme lipoprotein lipase. This may be related either to the urinary loss of some activators of the enzyme or to an increase in free fatty acids that are known to inhibit lipoprotein lipase activity. The reduction of HDL levels may be attributed to the urinary loss of lecithin-cholesterol acyltransferase and/or to its inhibition caused by the increased levels of free lysolecithin

produced in hypoalbuminemia. There has been controversy in the past about the possible role of hyperlipidemia in favoring cardiovascular complications. More recently an association between lipid abnormalities and coronary artery disease has been demonstrated in nephrotic patients. A lipid-lowering diet (<200 mg/day of cholesterol, total fat <30 % of total calories, and polyunsaturated fatty acids about 10 % of total calories) is usually recommended as the first therapeutic step in patients with hypercholesterolemia. However, for many nephrotic patients, diet is not sufficient to correct hyperlipidemia. Various lipid-lowering drugs such as probucol, nicotinic acid, resins, and fibric acid derivates have been used with little success because these agents are either poorly tolerated or have little efficacy. At present, hydroxymethylglutaryl coenzyme A (HMGCoA) reductase inhibitors are considered the drugs of choice for treating the hyperlipidemia of nephrotic patients. These agents may decrease serum cholesterol 30–40 %, LDL about 40 %, and apolipoprotein B 30 %, but do not reduce the elevated levels of the atherogenic LP(a). The tolerance is usually good. Mild and transient increase in serum transaminase is rarely seen. Myositis and myalgias are rare but can occur with large doses.

Edema

Edema is one of the cardinal features of the nephrotic syndrome. Its pathogenesis is incompletely understood. Two main theories have been proposed: the classical underfill theory and the overfill theory. According to the classical view, hypoalbuminemia represents the “primum movens” of edema. Decreased plasma oncotic pressure favors translocation of fluid from the intravascular space into interstitial space. Reduction of plasma volume activates the renin-angiotensin system, secondary salt and water retention, plasma dilution, and further aggravation of hypoalbuminemia. However, only aminority of

nephrotic patients have a decreased intravascular volume. The majority show normal or expanded plasma volume. Moreover, the plasma levels of renin, angiotensin, and aldosterone show large variations in nephrotic patients. Finally, maneuvers that increase plasma volume do not always result in a natriuretic response. The overfill theory attributes a key role to the inability of the diseased kidney to excrete salt and water, with consequent intravascular expansion, increase in capillary hydrostatic pressure, and transudation of fluid into the interstitial space. The enhanced tubular NaCl avidity is mainly caused by post-receptor resistance to the action of atrial natriuretic peptide, due to enhanced activity of cyclic GMP phosphodiesterase. Although the overfill theory may account for most cases of nephrotic edema, it is possible that underfill mechanisms are involved in few other cases, especially during the edema acquisition phase. In milder cases, edema may be handled by restricting dietary sodium intake. Diuretic therapy may be required in patients who do not respond to a low-sodium diet. The first step may consist of administration of hydrochlorothiazide (12.5–50 mg/day), preferably in combination with a potassium-sparing agent such as amiloride, triamterene, or spironolactone. Loop diuretics, such as furosemide, ethacrynic acid, or bumetanide are needed for more severe edema. Furosemide is the most-used agent because of its flexibility and good tolerance. The drug may be given by mouth or intravenously, at doses ranging between 25 and 2000 mg/day. Binding of the drug to tubular fluid albumin can blunt the diuretic response. In patients who do not respond to high-dose furosemide, combining it with diuretics acting at different levels, such as hydrochlorothiazide (25–50 mg/day) or metolazone (2.5–10 mg/day), may maximize the diuretic response.

Coagulation Abnormalities

In the nephrotic syndrome, there is an imbalance between procoagulant / antithrombotic factors. Usually there is an increase of prothrombotic factors such as fibrinogen, factors V and VIII, factor VII, platelets, and platelet hyperaggregability. Anticoagulant proteins such as active protein S, active protein C, antithrombin III are decreased, due to loss in the urine. In addition, nephrotic patients may show hyperviscosity favored by hyperlipidemia and impaired fibrinolysis, caused by elevated Lp(a) and ANG IV levels that promote the synthesis of plasminogen activation inhibitor. These hemostatic abnormalities promote the synthesis of plasminogen activation inhibitor and determine a hypercoagulable state that may cause thromboembolic complications. Renal vein thrombosis, deep vein thrombosis and pulmonary embolism are the most frequent thrombotic complications of the nephrotic syndrome and are roughly correlated with the magnitude of the depression of serum albumin. Their incidence is lower in children than in adults, but children are more exposed to the risk of arterial thrombosis. Anticoagulant drugs can reduce the risk of thrombosis. However, because they carry a substantial risk of hemorrhagic complications, their use is generally restricted to situations such as prolonged bed rest, surgery, and episodes of dehydration. On the other hand, decision analysis studies reported that the benefits of prophylactic anticoagulants outweigh the risks, at least in nephrotic patients with membranous nephropathy who are particularly exposed to the risk of intravascular thrombosis.

Infections

Nephrotic patients have an increased susceptibility to infections. Several factors may be responsible: urinary loss of

immunoglobulins, urinary loss of complement factors B and D, defective cellular immunity caused by the urinary loss of zinc, transferrin and vitamin D, and malnutrition. The concomitant use of high-dose glucocorticoids and immunosuppressive agents may further increase the risk of infections.

Endocrine Abnormalities

Nephrotic patients have significant urinary losses and reduced plasma concentration of 25(OH)D3. However, the vitamin D binding protein is also reduced in the nephrotic syndrome, so that the free 1,25(OH)2D3 remains at normal plasma levels. Hypocalcemia is frequently seen in nephrotic patients. In most cases, it may be attributed solely to the reduction in protein-bound calcium secondary to hypoalbuminemia. Thus, while many nephrotic patients may show decreased serum levels of 25(OH)D3 and calcium, the serum-free 1,25(OH)2D3 and ionized calcium are normal so that treatment with vitamin D is not necessary. However, vitamin D supplements are indicated in a minority of patients who demonstrate evidence of reduced serum ionized calcium, reduced intestinal calcium absorption, and secondary hyperparathyroidism. Urinary losses of thyroxin-binding globulin can occur in the nephrotic syndrome. However, the serum levels of T4 and thyrotropin are normal, and clinically most patients are euthyroid.

Pyelonephritis

Acute infections of the urinary tract fall into two general anatomic categories: lower tract infection (urethritis and cystitis) and upper tract infection (acute pyelonephritis, prostatitis, and intrarenal and perinephric abscesses). Infections at various sites may occur together or independently and may either be asymptomatic or present as one of the clinical syndromes

described in this chapter. Infections of the urethra and bladder are often considered superficial (or mucosal) infections, while prostatitis, pyelonephritis, and renal suppuration signify tissue invasion.

From a microbiologic perspective, urinary tract infection (UTI) exists when pathogenic microorganisms are detected in the urine, urethra, bladder, kidney, or prostate. In most instances, growth of 10^5 organisms per milliliter from a properly collected midstream "clean-catch" urine sample indicates infection. However, significant bacteriuria is lacking in some cases of true UTI. Especially in symptomatic patients, fewer bacteria (10^2–10^4/mL) may signify infection. In urine specimens obtained by suprapubic aspiration or "in-and-out" catheterization and in samples from a patient with an indwelling catheter, colony counts of 10^2–10^4/mL generally indicate infection. Conversely, colony counts of $>10^5$/mL in midstream urine are occasionally due to specimen contamination, which is especially likely when multiple bacterial species are found.

Infections that recur after antibiotic therapy can be due to the persistence of the originally infecting strain (as judged by species, antibiogram, serotype, and molecular type) or to reinfection with a new strain. "Same-strain" recurrent infections that become evident within 2 weeks of cessation of therapy can be the result of unresolved renal or prostatic infection (termed *relapse*) or of persistent vaginal or intestinal colonization leading to rapid reinfection of the bladder.

Symptoms of dysuria, urgency, and frequency that are unaccompanied by significant bacteriuria have been termed the *acute urethral syndrome*. Although widely used, this term lacks anatomic precision because many cases so designated are actually bladder infections. Moreover, since the pathogen can usually be identified, the term *syndrome* - implying unknown causation - is inappropriate.

Chronic pyelonephritis refers to chronic interstitial

nephritis believed to result from bacterial infection of the kidney. Many noninfectious diseases also cause an interstitial nephritis that is indistinguishable pathologically from chronic pyelonephritis.

Etiology

Many microorganisms can infect the urinary tract, but by far the most common agents are the gram-negative bacilli. *Escherichia coli* cause ~80 % of acute infections (both cystitis and pyelonephritis) in patients without catheters, urologic abnormalities, or calculi. Other gram-negative rods, especially *Proteus* and *Klebsiella* spp. and occasionally *Enterobacter* spp., account for a smaller proportion of uncomplicated infections. These organisms, along with *Serratia* spp. and *Pseudomonas* spp., assume increasing importance in recurrent infections and in infections associated with urologic manipulation, calculi, or obstruction. They play a major role in nosocomial, catheter-associated infection. *Proteus* spp. (through the production of urease) and *Klebsiella* spp. (through the production of extracellular slime and polysaccharides) predispose to stone formation and are isolated more frequently from patients with calculi.

Gram-positive cocci play a lesser role in UTIs. However, *Staphylococcus saprophyticus* - a novobiocin-resistant, coagulase-negative species - accounts for 10–15 % of acute symptomatic UTIs in young female patients. Enterococci occasionally cause acute uncomplicated cystitis in women. More commonly, enterococci and *Staphylococcus aureus* cause infections in patients with renal stones or with previous instrumentation or surgery. Isolation of *S. aureus* from the urine should arouse suspicion of bacteremic infection of the kidney. *Staphylococcus epidermidis* is a common cause of catheter-associated UTI.

About one-third of women with dysuria and frequency have either an insignificant number of bacteria in midstream urine cultures or completely sterile cultures and have been previously defined as having the urethral syndrome. About three-quarters of these women have pyuria, while one-quarter have no pyuria and little objective evidence of infection. In the women with pyuria, two groups of pathogens account for most infections. Low counts (10^2–10^4/mL) of typical bacterial uropathogens such as *E. coli*, *S. saprophyticus*, *Klebsiella*, or *Proteus* are found in midstream urine specimens from most of these women. These bacteria are probably the causative agents in these infections because they can usually be isolated from a suprapubic aspirate, are associated with pyuria, and respond to appropriate antimicrobial therapy. In other women with acute urinary symptoms, pyuria, and urine that is sterile (even when obtained by suprapubic aspiration), sexually transmitted urethritis-producing agents such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and herpes simplex virus (HSV) are etiologically important. These agents are found most frequently in young, sexually active women with new sexual partners.

The causative role of several more unusual bacterial and nonbacterial pathogens in UTIs remains poorly defined. *Ureaplasma urealyticum* has frequently been isolated from the urethra and urine of patients with acute dysuria and frequency but is also found in specimens from many patients without urinary symptoms. Ureaplasmas and *Mycoplasma genitalium* probably account for some cases of urethritis and cystitis. *U. urealyticum* and *Mycoplasma hominis* have been isolated from prostatic and renal tissues of patients with acute prostatitis and pyelonephritis, respectively, and are probably responsible for some of these infections as well. Adenoviruses cause acute hemorrhagic cystitis in children and in some young adults, often in epidemics. Although other viruses can be isolated from urine (e.g. cytomegalovirus), they are thought not to cause acute UTI.

Colonization of the urine of catheterized or diabetic patients by *Candida* and other fungal species is common and sometimes progresses to symptomatic invasive infection.

Pathogenesis and Sources of Infection

The urinary tract should be viewed as a single anatomic unit that is united by a continuous column of urine extending from the urethra to the kidney. In the vast majority of UTIs, bacteria gain access to the bladder via the urethra. Ascent of bacteria from the bladder may follow and is probably the pathway for most renal parenchymal infections.

The vaginal introitus and distal urethra are normally colonized by diphtheroids, streptococcal species, lactobacilli, and staphylococcal species but not by the enteric gram-negative bacilli that commonly cause UTIs. In females prone to the development of cystitis, however, enteric gram-negative organisms residing in the bowel colonize the introitus, the periurethral skin, and the distal urethra before and during episodes of bacteriuria. The factors that predispose to periurethral colonization with gram-negative bacilli remain poorly understood, but alteration of the normal vaginal flora by antibiotics, other genital infections, or contraceptives (especially spermicide) appears to play an important role. Loss of the normally dominant H_2O_2-producing lactobacilli from the vaginal flora appears to facilitate colonization by *E. coli*. Small numbers of periurethral bacteria probably gain entry to the bladder frequently, and this process is facilitated in some cases by urethral massage during intercourse. Whether bladder infection ensues depends on interacting effects of strain pathogenicity, inoculum size, and local and systemic host defense mechanisms. Recent data from both animal models and human studies indicate that *E. coli* sometimes invades the bladder epithelium, forming intracellular colonies (biofilms) that may persist and become a source of recurrent infection.

Under normal circumstances, bacteria placed in the bladder are rapidly cleared, partly through the flushing and dilutional effects of voiding but also as a result of the antibacterial properties of urine and the bladder mucosa. Owing mostly to a high urea concentration and high osmolarity, the bladder urine of many healthy persons inhibits or kills bacteria. Prostatic secretions possess antibacterial properties as well. Bladder epithelial cells secrete cytokines and chemokines - primarily interleukin (IL) 6 and IL-8 - upon interaction with bacteria, causing polymorphonuclear leukocytes to enter the bladder epithelium and the urine soon after infection arises and play a role in clearing bacteriuria. The role of locally produced antibody remains unclear.

Hematogenous pyelonephritis occurs most often in debilitated patients who are either chronically ill or receiving immunosuppressive therapy. Metastatic staphylococcal or candidal infections of the kidney may follow bacteremia or fungemia, spreading from distant foci of infection in the bone, skin, or vasculature or elsewhere.

Conditions Affecting Pathogenesis

Gender and Sexual Activity. The female urethra appears to be particularly prone to colonization with colonic gram-negative bacilli because of its proximity to the anus, its short length (~4 cm), and its termination beneath the labia. Sexual intercourse causes the introduction of bacteria into the bladder and is temporally associated with the onset of cystitis; it thus appears to be important in the pathogenesis of UTIs in both pre- and postmenopausal women. Voiding after intercourse reduces the risk of cystitis, probably because it promotes the clearance of bacteria introduced during intercourse. Use of spermicidal compounds with a diaphragm or cervical cap or use of spermicide-coated condoms dramatically alters the normal introital bacterial flora and has

been associated with marked increases in vaginal colonization with *E. coli* and in the risk of both cystitis and acute pyelonephritis. In healthy, community-dwelling postmenopausal women, the risk of UTI (both cystitis and pyelonephritis) is increased by a history of recent sexual activity, recent UTI, diabetes mellitus, and incontinence.In male patients who are <50 years old and who have no history of heterosexual or homosexual insertive rectal intercourse, UTI is exceedingly uncommon, and this diagnosis should be questioned in the absence of clear documentation. An important factor predisposing to bacteriuria in men is urethral obstruction due to prostatic hypertrophy. Insertive rectal intercourse is also associated with an increased risk of cystitis in men. Men (and women) who are infected with HIV and who have CD4+ T cell counts of <200/L are at increased risk of both bacteriuria and symptomatic UTI. Finally, lack of circumcision has been identified as a risk factor for UTI in both male neonates and young men.

Pregnancy. UTIs are detected in 2–8 % of pregnant women. Symptomatic upper tract infections, in particular, are unusually common during pregnancy; fully 20–30 % of pregnant women with asymptomatic bacteriuria subsequently develop pyelonephritis. This predisposition to upper tract infection during pregnancy results from decreased ureteral tone, decreased ureteral peristalsis, and temporary incompetence of the vesicoureteral valves. Bladder catheterization during or after delivery causes additional infections. Increased incidences of low birth weight, premature delivery, and neonatal death result from UTIs (particularly upper tract infections) during pregnancy.

Obstruction. Any impediment to the free flow of urine - tumor, stricture, stone, or prostatic hypertrophy - results in hydronephrosis and a greatly increased frequency of UTI. Infection superimposed on urinary tract obstruction may

lead to rapid destruction of renal tissue. It is of utmost importance, therefore, when infection is present, to identify and repair obstructive lesions. On the other hand, when an obstruction is minor and is not progressive or associated with infection, great caution should be exercised in attempting surgical correction. The introduction of infection in such cases may be more damaging than an uncorrected minor obstruction that does not significantly impair renal function.

Neurogenic Bladder Dysfunction. Interference with bladder enervation, as in spinal cord injury, tabes dorsalis, multiple sclerosis, diabetes, and other diseases, may be associated with UTI. The infection may be initiated by the use of catheters for bladder drainage and is favored by the prolonged stasis of urine in the bladder. An additional factor often operative in these cases is bone demineralization due to immobilization, which causes hypercalciuria, calculus formation, and obstructive uropathy.

Vesicoureteral Reflux. Defined as reflux of urine from the bladder cavity up into the ureters and sometimes into the renal pelvis, vesicoureteral reflux occurs during voiding or with elevation of pressure in the bladder. In practice, this condition is detected as retrograde movement of radiopaque or radioactive material during a voiding cystourethrogram. An anatomically impaired vesicoureteral junction facilitates reflux of bacteria and thus upper tract infection. However, since - even in the healthy urinary system - a fluid connection between the bladder and the kidneys always exists, some retrograde movement of bacteria probably takes place during infection but is not detected by radiologic techniques.

Vesicoureteral reflux is common among children with anatomic abnormalities of the urinary tract or with anatomically normal but infected urinary tracts. In the latter group, reflux disappears with advancing age and is probably attributable to factors other than UTI. Long-term follow-up of

children with UTI who have reflux has established that renal damage correlates with marked reflux, not with infection. Thus, it appears reasonable to search for reflux in children with unexplained failure of renal growth or with renal scarring, because UTI per se is an insufficient explanation for these abnormalities. On the other hand, it is doubtful that all children who have recurrent UTIs but whose urinary tract appears normal on pyelography should be subjected to voiding cystoureterography merely for the detection of the rare patient with marked reflux not revealed by intravenous pyelography.

Bacterial Virulence Factors. Not all strains of *E. coli* are equally capable of infecting the intact urinary tract. Bacterial virulence factors markedly influence the likelihood that a given strain, once introduced into the bladder, will cause UTI. Most *E. coli* strains that cause symptomatic UTIs in noncatheterized patients belong to a small number of specific O, K, and H serogroups. These uropathogenic clones have accumulated a number of virulence genes that are often closely linked on the bacterial chromosome in "pathogenicity islands." Bacterial adherence to uroepithelial cells is a critical first step in the initiation of infection. For both *E. coli* and *Proteus* spp., fimbriae (hairlike proteinaceous surface appendages) mediate bacterial attachment to specific receptors on epithelial cells, which in turn initiates important events in the mucosal epithelial cell, including secretion of IL-6 and IL-8 (with subsequent chemotaxis of leukocytes to the bladder mucosa) and induction of apoptosis and epithelial cell desquamation. Besides fimbriae, uropathogenic *E. coli* strains usually produce cytotoxins, hemolysin, and aerobactin (a siderophore for scavenging iron) and are resistant to the bactericidal action of human serum. Nearly all *E. coli* strains causing acute pyelonephritis and most of those causing acute cystitis are uropathogenic strains possessing pathogenicity islands. In contrast, infections in patients with structural or functional

abnormalities of the urinary tract are generally caused by bacterial strains that lack these uropathogenic properties; the implication is that these properties are not needed for infection of the compromised urinary tract.

Genetic Factors. Increasing evidence suggests that host genetic factors influence susceptibility to UTI. A maternal history of UTI is more often found among women who have experienced recurrent UTIs than among controls. The number and type of receptors on uroepithelial cells to which bacteria may attach are, at least in part, genetically determined. Many of these structures are components of blood group antigens and are present on both erythrocytes and uroepithelial cells. For example, P fimbriae mediate attachment of *E. coli* to P-positive erythrocytes and are found on nearly all strains causing acute uncomplicated pyelonephritis. Conversely, P blood group–negative individuals, who lack these receptors, are at decreased risk of pyelonephritis. Furthermore, nonsecretors of blood group antigens are at increased risk of recurrent UTI; this predisposition may relate to a different profile of genetically determined glycolipids on uroepithelial cells. Mutations in host genes integral to the immune response (e.g. Toll-like receptors, interferon receptors) may also affect susceptibility to UTI.

Diagnostic Testing

Determination of the number and type of bacteria in the urine is an extremely important diagnostic procedure. In symptomatic patients, bacteria are usually present in the urine in large numbers (10^5/mL). In asymptomatic patients, two consecutive urine specimens should be examined bacteriologically before therapy is instituted, and 10^5 bacteria of a single species per milliliter should be demonstrable in both specimens. Since the large number of bacteria in the bladder urine is due in part to bacterial multiplication in the bladder cavity, samples of urine from the ureters or renal pelvis may

contain $<10^5$ bacteria per milliliter and yet indicate infection. Similarly, the presence of bacteriuria of any degree in suprapubic aspirates or of 10^2 bacteria per milliliter of urine obtained by catheterization usually indicates infection. In some circumstances (antibiotic treatment, high urea concentration, high osmolarity, low pH), urine inhibits bacterial multiplication, resulting in relatively low bacterial colony counts despite infection. For this reason, antiseptic solutions should not be used to wash the periurethral area before collection of the urine specimen. Water diuresis or recent voiding also reduces bacterial counts in urine.

Microscopy of urine from symptomatic patients can be of great diagnostic value. Microscopic bacteriuria, which is best assessed with Gram-stained uncentrifuged urine, is found in >90% of specimens from patients whose infections are associated with colony counts of at least 10^5/mL, and this finding is very specific. However, bacteria cannot usually be detected microscopically in infections with lower colony counts (10^2–10^4/mL). The detection of bacteria by urinary microscopy thus constitutes firm evidence of infection, but the absence of microscopically detectable bacteria does not exclude the diagnosis. When carefully sought by chamber-count microscopy, pyuria is a highly sensitive indicator of UTI in symptomatic patients. Pyuria is demonstrated in nearly all acute bacterial UTIs, and its absence calls the diagnosis into question. The leukocyte esterase "dipstick" method is less sensitive than microscopy in identifying pyuria but is a useful alternative when microscopy is not feasible. Pyuria in the absence of bacteriuria (sterile pyuria) may indicate infection with unusual agents such as *C. trachomatis*, *U. urealyticum*, or *Mycobacterium tuberculosis* or with fungi. Alternatively, sterile pyuria may be documented in noninfectious urologic conditions such as calculi, anatomic abnormality,

nephrocalcinosis, vesicoureteral reflux, interstitial nephritis, or polycystic disease.

Although many authorities have recommended that urine culture and antimicrobial susceptibility testing be performed for any patient with a suspected UTI, it is more practical and cost-effective to manage women who have symptoms characteristic of acute uncomplicated cystitis without an initial urine culture. Two approaches to presumptive therapy have generally been used. In the first, treatment is initiated solely on the basis of a typical history and/or typical findings on physical examination. In the second, women with symptoms and signs of acute cystitis and without complicating factors are managed with urinary microscopy (or, alternatively, with a leukocyte esterase test). A positive result for pyuria and/or bacteriuria provides enough evidence of infection to omit urine culture and susceptibility testing and treat the patient empirically. Urine should be cultured, however, when a woman's symptoms and urine-examination findings leave the diagnosis of cystitis in question. Pretherapy cultures and susceptibility testing are also essential in the management of all patients with suspected upper tract infections and of those with complicating factors (including all men). In these situations, any of a variety of pathogens may be involved, and antibiotic therapy is best tailored to the individual organism.

Urologic Evaluation

Very few women with recurrent UTIs have correctable lesions discovered at cystoscopy or upon IV pyelography, and these procedures should not be undertaken routinely in such cases. Urologic evaluation should be performed for selected female patients - namely, women with relapsing infection, a history of childhood infections, stones or painless hematuria, or recurrent pyelonephritis. Most male patients with UTI should be considered to have complicated infection and thus should be

evaluated urologically. Possible exceptions include young men who have cystitis associated with sexual activity, who are uncircumcised, or who have AIDS. Men or women presenting with acute infection and signs or symptoms suggestive of an obstruction or stones should undergo prompt urologic evaluation, generally by means of ultrasound.

Treatment

The following principles underlie the treatment of UTIs:

1 Except in acute uncomplicated cystitis in women, a quantitative urine culture or a comparable alternative diagnostic test should be performed to confirm infection before empirical treatment is begun, and antimicrobial sensitivity testing should be used to direct therapy.

2 Factors predisposing to infection, such as obstruction and calculi, should be identified and corrected if possible.

3 Relief of clinical symptoms does not always indicate bacteriologic cure.

4 Each course of treatment should be classified after its completion as a failure (symptoms and/or bacteriuria not eradicated during therapy or in the immediate posttreatment culture) or a cure (resolution of symptoms and elimination of bacteriuria). Recurrent infections should be classified as same-strain or different-strain and as early (occurring within 2 weeks of the end of therapy) or late.

5 In general, uncomplicated infections confined to the lower urinary tract respond to short courses of therapy, while upper tract infections require longer treatment. After therapy, early recurrences due to the same strain may result from an unresolved upper tract focus of infection but often (especially after short-course therapy for cystitis) result from persistent vaginal colonization. Recurrences >2 weeks after the cessation of therapy nearly always represent reinfection with a new strain

or with the previously infecting strain that has persisted in the vaginal and rectal flora.

6 Despite increasing resistance, community-acquired infections (especially initial infections) are usually due to relatively antibiotic-sensitive strains.

7 In patients with repeated infections, instrumentation, or recent hospitalization, the presence of antibiotic-resistant strains should be suspected. Although many antimicrobial agents reach high concentrations in urine, in vitro resistance usually predicts a substantially higher failure rate.

Antibiotic Choice

Antibiotic choices for the treatment of pyelonephritis depend upon the severity of symptoms, the causative organisms, and the presence or absence of complicating factor. For mild cases of pyelonephritis, outpatient therapy with oral antibiotics such as TMP-SMX or fluoroquinolones in the same doses prescribed for cystitis but continued for 2 weeks may be sufficient. If hospitalization and parenteral therapy are required, options for treatment of uncomplicated pyelonephritis include:

Table 2 - Treatment Options for Pyelonephritis

Entity	**Drug**	**Duration**
Subclinical or mild-moderate pyelonephritis	TMP-SMX 1 DS tab PO BID Ciprofloxacin 500 mg PO BID (or other fluoroquinolones)	14 days (outpatient)
Moderate-severe pyelonephritis	*Enterococcus:* IV ampicillin ± gentamicin; Gram-negative bacteria: IV fluoro- quinolone, third-generation cephalosporin, aztreonam or gentamicin	IV therapy until clinically stable (inpatient initially), then complete 14-day course

Continuation of Table 2

Entity	**Drug**	**Duration**
Complicated pyelonephritis	IV broad spectrum antibiotics, usually to include agents active against *Pseudomonas*, especially if nosocomial or nursing home-acquired infection	IV therapy until stable, followed by oral drugs to complete a minimum of 14 days; longer therapy may be necessary

Other possible agents include imipenem or other broad-spectrum antibiotics. The choice of antibiotics should be adjusted as indicated by the infecting organism's susceptibility pattern, when available. For hospitalized patients, parenteral antibiotics should be continued until the patient is stable, after which oral antibiotics can usually be used to complete the treatment. Care must be exercised in the choice of antibiotics for pregnant women. Fluoroquinolones should be avoided in pregnant women (and in children) because of concerns about their effect on cartilage development. Aminoglycosides should be used with caution due to the possibility of fetal cranial nerveVIII damage, and TMP-SMXshould be avoided near term to avoid kernicterus in the baby. Tetracyclines are contraindicated in children and pregnant women. Duration of Therapy The optimal duration of therapy for pyelonephritis has not been well studied. Although treatment for as long as 6 weeks has traditionally been advocated, >2 weeks of treatment is usually not necessary for uncomplicated cases. Fortunately, the availability of oral fluoroquinolones increases the ease of IV to PO switching and again allows earlier discharge from the hospital. Therapy for >14 days may be necessary in selected cases of complicated pyelonephritis or in men if prostatic infection is suspected.

Prognosis

With appropriate antimicrobial therapy, the prognosis for patients with pyelonephritis is complete recovery. In patients who fail to respond clinically after 72 hours of therapy with appropriate antibiotics, additional evaluation is indicated. Careful review of antibiotic sensitivity based on culture results should be undertaken. Radiographic imaging to rule out obstruction, anatomic abnormalities, or intrarenal or perinephric abscesses can be considered. Renal ultrasound, CT scans and possibly an intravenous pyelogram (IVP) may be necessary to detect abnormalities requiring surgical intervention. Careful follow-up of patients with pyelonephritis is important, but the specifics of the required evaluation are unclear. At the least, instructions to return if symptoms recur is critical. The role of follow-up office visits, urinalysis, or urine culture is undefined. Follow- up “test of cure” urine cultures should be done within 1–2 weeks of completion of therapy in pregnant.

TUBULOINTERSTITIAL NEPHRITIS

Primary tubulointerstitial diseases of the kidney are characterized by histologic and functional abnormalities that involve the tubules and interstitium to a greater degree than the glomeruli and renal. Secondary tubulointerstitial disease occurs as a consequence of progressive glomerular or vascular injury. Morphologically, acute forms of these disorders are characterized by interstitial edema, often associated with cortical and medullary infiltration by both mononuclear cells and polymorphonuclear leukocytes, and patchy areas of tubule cell necrosis. In more chronic forms, interstitial fibrosis predominates, inflammatory cells are typically mononuclear, and abnormalities of the tubules tend to be more widespread, as evidenced by atrophy, luminal dilatation, and thickening of tubule basement membranes. Because of the nonspecific nature of the histology, particularly in chronic tubulointerstitial diseases, biopsy specimens rarely provide a specific diagnosis. The urine sediment is also unlikely to be diagnostic, except in allergic forms of acute tubulointerstitial disease in which eosinophils may predominate in the urinary sediment.

Table 3 - Principal Causes of Tubulointerstitial Disease of the Kidney

Acute Interstitial Nephritis
Drugs
Antibiotics (sulfonamides, quinolones, vancomycin, erythromycin, minocycline, rifampin, ethambutol, acyclovir)
Nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors
Diuretics (thiazides, furosemide, triamterene)
Anticonvulsants (phenytoin, phenobarbital, carbamazepine, valproic acid)

Continuation of Table 3

Miscellaneous (captopril, H_2 receptor blockers, proton pump inhibitors, mesalazine, indinavir, allopurinol)
Infection
Bacteria (*Streptococcus*, *Staphylococcus*, *Legionella*, *Salmonella*, *Brucella*, *Yersinia*, *Corynebacterium diphtheriae*)
Viruses (Epstein-Barr virus, cytomegalovirus, Hantavirus, polyomavirus, HIV)
Miscellaneous (*Leptospira*, *Rickettsia*, *Mycoplasma*)
Idiopathic
Tubulointerstitial nephritis–uveitis syndrome
Anti-tubule basement membrane disease
Sarcoidosis
Chronic Tubulointerstitial Diseases
Hereditary renal diseases
Polycystic kidney
Medullary cystic disease
Medullary sponge kidney
Exogenous toxins
Analgesic nephropathy[a]
Lead nephropathy
Miscellaneous nephrotoxins (e.g., lithium[a], cyclosporine[a], heavy metals, slimming regimens with Chinese herbs)
Metabolic toxins
Hyperuricemia[a]
Hypercalcemia
Miscellaneous metabolic toxins (e.g., hypokalemia, hyperoxaluria, cystinosis, Fabry's disease)
Autoimmune disorders
Sjögren's syndrome

Continuation of Table 3

Neoplastic disorders
Leukemia
Lymphoma
Multiple myeloma[a]
Miscellaneous disorders
Sickle cell nephropathy
Chronic pyelonephritis
Chronic urinary tract obstruction
Vesicoureteral reflux[a]
Radiation nephritis
Balkan nephropathy
Tubulointerstitial disease secondary to glomerular and vascular disease

Mechanisms of Tubulointerstitial Nephritis

The tubulointerstitial compartment accounts for 80 % of the renal mass. It consists of renal tubuli, the tubular basement membrane, vascular structures, and interstitial cells as well as the surrounding extracellular matrix. The interstitial cells can be divided mainly into renal fibroblast cells and cells of the monocyte/macrophage system including dendritic cells. The tubulointerstitial compartment is involved in the course of almost all renal diseases. As a rule, changes begin with an interstitial inflammation that is the hallmark of tubulointerstitial nephritis (TIN). TIN can exist in an acute and a chronic form and can affect the tubulointerstitial space primarily or in the setting of primary glomerular or vascular diseases. All forms of interstitial disease are quite common. It has been estimated that up to 15 % of all cases of acute renal failure (ARF) are caused by primary interstitial nephritis. In addition, up to 25 % of all cases of end-stage renal disease (ESRD) are attributable to primary chronic TIN. According to

the European Dialysis and Transplant Association (EDTA) registry, 20.2 % of ESRD was caused either by pyelonephritis, interstitial nephritis, or toxic nephropathy. These forms are characterized by primary TIN. More recent data, however, suggest a less prominent role,with about 4.5 % of cases of chronic renal failure (CRF) in the US attributable to primary interstitial diseases. Moreover, secondary tubulointerstitial injury is one of the most important factors for the outcome of primary glomerular and vascular diseases because interstitial nephritis is the common pathway of almost all forms of progressive renal disease and one of the most common lesions in nephrology. Immune response in interstitial nephritis can be antibody dependent or cell mediated but, in contrast to glomerular diseases, cell-mediated reactions predominate. In TIN, T lymphocytes are the predominant infiltrating cells with a great abundance of CD4+ T helper cells (CD4/CD8-ratio often >1). These T helper cells need MHC-class II (HLA-D) restricted presentation of responsible antigens to become activated. Antigen presentation in the renal interstitium can be provided efficiently by infiltrating macrophages and interstitial dendritic cells. In addition, data on glomerular diseases suggest that tubular epithelial cells may serve as antigen presenters as well. In interstitial nephritis, predominantly CD8+ T effector cells become activated in turn and result in renal tissue damage by 2 mechanisms: they can be cytotoxic due to the release of perforans, or they can lead to a delayed-type hypersensitivity reaction with the release of inflammatory cytokines. Only occasionally, deposition of immune complexes within the interstitium may be found, especially in patients with underlying systemic autoimmune disorders. In rare cases of specific antitubular basement membrane disease, linear deposition of immunoglobulin along the tubular basement membrane can be detected (additionally in up to 70 % of cases with primary antiglomerular basement membrane (anti-GBM)

disease). The target antigens for humoral immunity in human TIN remain poorly defined. Only the target antigen of experimental antitubular basement membrane (TBM) disease in mice has been characterized as glycoprotein 3M-1 and is secreted by proximal tubular cells. Apart from native renal antigens, drug/hapten conjugates, microbial antigens, and foreign antigens that induce crossreactive immunity to autoantigens (molecular mimicry) are believed to be of importance in TIN. Irrespective of the type of immune reaction, in the course of sustained primary or secondary interstitial inflammation and tissue damage, activation of interstitial cells can initiate processes of interstitial proliferation and fibrogenesis that inevitably result in renal scarring and chronic renal failure. Figure 1 summarizes the pathogenesis and clinical manifestations of TIN.

Clinical Features

In ATIN, a rapid decrease in renal function is typical at presentation. A careful evaluation of the history is essential in this setting because most patients will be asymptomatic or will complain only of unspecific symptoms. For example, the clinician should be on the alert for a new medication, especially in the elderly patient, or systemic illness, particularly streptococcal infections in children. While there are no pathognomonic clinical findings in ATIN, certain systemicmanifestations may point to the diagnosis if present. The classical descriptions of patients with methicillin-induced interstitial nephritis go back to the early 1960s. Systemic manifestations such as – low-grade fever (70–100 %), – fleeting skin rash (30–50 %), and – diffuse arthralgias (up to 20 %) together with signs of ARF make ATIN a probable diagnosis. However, the entire constellation has been reported in the minority of ATIN cases (4 out of 27 in one study). In

most cases only nonspecific constitutional symptoms such as fever, fatigue, or nausea are present. In addition, some patients may complain of lumbar pain due to distension of the renal capsule from diffuse swelling of the kidney. In contrast to glomerular diseases, oliguria, edema, and hypertension are less common in ATIN. As a consequence of an impaired tubular reabsorptive capacity, polyuria and nocturia may develop. Long-term consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to a type of ATIN, accompanied by glomerular proteinuria sometimes severe enough to cause full-blown nephrotic syndrome. ATIN histologically characterized by granuloma formation within the interstitium can clinically appear months after drug ingestion. Typically, classic allergic symptoms are lacking. Therefore, diagnosis is often delayed in these cases, and progression to renal failure often occurs.

Laboratory Findings

The first clinical presentation of ATIN is variable, and specific findings that point to diagnosis are often lacking. Several findings on blood and especially urine analysis may point of ATIN. Elevated plasma creatinine and blood urea nitrogen (BUN) values should be investigated to discover the cause of impaired renal function. Especially in drug-related ATIN, further blood tests may reveal transient eosinophilia and elevated plasma IgE levels, but these findings occur only in about 30 % of cases. In addition, nonspecific elevations of C-reactive protein (CRP) levels and an accelerated erythrocyte sedimentation rate (ESR) may be present. In >75 % of cases, mild to moderate proteinuria and hematuria can be found. Proteinuria is tubular in the majority of cases. Nephrotic-range proteinuria is not usually found. However, NSAID-induced interstitial nephritis is often characterized by serious renal injury including the glomeruli (minimal change lesions).

Hence, this form of ATIN may be accompanied by nephrotic syndrome. Gross hematuria rarely occurs in ATIN, but careful examination of the urinary sediment is essential. In approximately 75 % of patients, red and white blood cells (sterile pyuria) will be found. Occasionally, white and red blood cell casts may be observed, but the latter strongly suggest a glomerular lesion. Eosinophiluria is suggestive of allergic interstitial nephritis. Eosinophils in the urine can be detected by either Wright's stain or Hansel's stain, the latter being approximately 5 times more sensitive. However, eosinophiluria can be observed in many other cases such as rapid progressive glomerulonephritis (GN), urinary tract infections (UTI), prostatitis, and atheroembolic disease, as well as in episodes of renal allograft rejection. Therefore, it may help to distinguish ATIN from acute tubular necrosis (ATN), but the positive predictive value of this parameter is <40 % according to recent studies. As a consequence of tubular injury and interstitial inflammation, various tubular dysfunctions may be observed in the course of ATIN. Lesions affecting the proximal tubule may result in glucosuria, aminoaciduria, uricosuria, and hyperphosphaturia. A proximal loss of bicarbonate along with an impaired acid secretion within the distal segments can result in renal tubular acidosis. Hyperkalemia and renal salt wasting together with a reduction of renal concentration ability may point to a dysfunction of the distal tubule or collecting duct. In a report of 9 patients with biopsyproven ATIN, isosthenuria was present in all patients with amean urinary osmolality <350 mOsm/L and a urine/plasma osmolality ratio of 0.9. Urinary sodium was >40 mEq/L in 8 out of the 9 patients studied. However, signs of tubule dysfunction such as Fanconi syndrome and renal tubular acidosis are rarely observed in the course of ATIN and are more common in patients with chronic tubulointerstitial disease.

Laboratory Features of ATIN

Blood Eosinophilia
IgE-Elevation
Proteinuria <3 g/day (exception: some cases of NSAID)
Tubular pattern (1-microglobulin, 2-microglobulin, N-acetyl-beta-lucosaminidase)
Sediment White blood cells (free and casts)
Microhematuria (rarely gross hematuria, red casts uncommon)
Eosinophilia
Functional Glucosuria, aminoaciduria, hyperphosphaturia parameters
Renal tubular acidosis (bicarbonate loss, impaired acid secretion)
Hyperkalemia
Salt wasting
Impaired concentration ability

Diagnosis

Tubulointerstitial nephritis is a pathological phenomenon and not a clinical syndrome. Many features in clinical presentation and in laboratory analysis may suggest ATIN but only renal biopsy can establish the diagnosis with certainty in this setting. Therefore, renal biopsy should always be considered in any patients with ARF of unknown origin. Ultrasonography is useful in the detection of ATIN. Because of the increased interstitial volume, the kidneys may appear swollen and the cortical echogenicity may be increased. Additionally, renal scanning with gallium-67 has also been reported to detectATINin some patients. This method is very sensitive; however, the specificity is relatively low. Therefore,

this method is not reliable in identifying noninfectious interstitial nephritis.

Chronic Tubulointerstitial Nephritis (CTIN)

Pathology

The pathological findings in patients withchronic forms of tubulointerstitial nephritis display characteristic changes in interstitialarchitecture observed in virtually all forms of chronic renal injury, e.g., of primary glomerular, vascular, cystic, or interstitial origin. Interstitial fibrosis along with tubular atrophy are the hallmarks of chronic interstitial disease. As an expression of ongoing inflammation, mononuclear cell infiltrates (mainly lymphocytes) in the interstitium and within the tubular epithelium (tubulitis with resulting cellular casts) can be seen. Although in CTIN the glomeruli mainly remain unaffected by the primary lesion, signs of secondary glomerular injury may be found as the disease progresses towards ESRD.

Clinical Features

Usually, CTIN does not cause any specific clinical symptoms unless a primary systemic disease is present. Hence, some cases are diagnosed because of findings in screening tests (abnormal urinalysis or elevations in plasma creatinine andBUN). However, many patients unfortunately present with nonspecific symptoms of chronic renal failure late in the course of the disease.

Laboratory Findings

When patients with CTIN present late, they have marked impairment of renal function and typical laboratory findings of chronic renal failure. Focal dense lymph/plasma

cell infiltration (PAS, magnification x 400) with nonnephrotic-range proteinuria of a predominant tubular protein pattern and microscopic hematuria as well as pyuria is observed. Surprisingly, positive urine cultures can be found many as 28 % of patients. As with acute TIN, glucosuria, renal tubular acidosis (RTA), and concentration defects reflect the degree of tubular dysfunction. Anemia develops relatively early (compared to glomerular diseases), and systemic hypertension occurs in about 50 % of cases.

Diagnosis

Renal biopsy is the only means for definite diagnosis in all forms of TIN, whether acute or chronic. Neither clinical features nor laboratoryfindings are specific. In CTIN associated with a primary disease, diagnosis may be suggestive in many cases but biopsy is still ofgreat value, especially for informed judgement on individual prognosis and required therapeutic decisions. Nevertheless, a thorough investigation of the patient's history will provide the only reasonable basis for diagnosis in many patients with established latestage renal failure.

Etiologic Factors

CTIN can occur in association with a variety of underlying primary diseases of diverse etiology.

Endemic nephropathy, so-called Balkan nephritis, is a form of CTIN that is endemic in areas of the Balkan states. Usually, the disease occurs in middle-aged adults and progresses slowly towards ESRD. No diagnostic tests are available, and its cause remains unknown (environmental agents, infections, and genetic factors are proposed). A higher incidence of uroepithelial tumors is suggested in these patients. As with other forms of TIN, elevated excretion of tubular

proteins (especially 2- microglobulin) as well as additional signs of tubular dysfunction can be observed early inasymptomatic patients. At this time there is no specific treatment regimen that can alter the rate of progression towards renal failure. hus, elimination of known progression factors is essential.

Most commonly, aberrations of calcium metabolism, including hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis, are responsible for the renal manifestations of sarcoidosis. Recent studies suggest that the calcium abnormalities are associated with high blood concentrations of calcitriol and that calcitriol may be synthesized by mononuclear macrophages in the granulomas. Up to one-third of patients with sarcoidosis are reported to have granulomas within the renal interstitium, which may also produce severe derangements of renal function. GN can occur with sarcoidosis, although the pathogenesis remains unclear. Clinically apparent kidney dysfunction is rare unless hypercalcemia and hypercalciuria are present (about 10–15 % of all patients). Mild to moderate albuminuria, microscopic hematuria, and sterile pyuria predominate. A protein excretion of >3 g/24 hours may indicate a concomitant glomerular lesion. Hypertension is usually absent and renal size is well preserved. Urinary concentration defects (including nephrogenic diabetes insipidus), renal tubular acidosis, and inappropriate glucosuria may also be seen. In patients with sarcoidosis-associated granulomatous TIN, renal disease is usually accompanied by other organ involvement. No factors are known to identify patients at high risk, but men are reported to be more prone to develop this entity. The findings in renal biopsy are distinct from other forms of TIN. Interstitial inflammation with noncaseating granulomas and epithelioid and multinucleated giant cells is the usual histologic picture. There is no positivity for complement or immunoglobulins. Rarely, nonspecific

glomerular or vasculitic changes can be observed. Pathologically, other granulomatous inflammatory processes like silicosis, tuberculosis, histoplasmosis, and Wegener granulomatosis or scattered infiltration by lymphoma cells (with reactive granuloma formation) may have to be distinguished in single cases. Interestingly, in a series of 6 patients with sarcoidosis and clinically significant renal insufficiency, 4 patients differed from the typical patient with sarcoidosis in that they lacked the usual clinical constellation of skin, eye, and pulmonary involvement. The diagnosis is supported by clinical findings of sarcoidosis involvement of other organs and should be suspected on the basis of elevated or paradoxically normal serum calcium concentrations, due to increased plasma concentrations of calcitriol, while immunoreactive circulating parathormone concentra- tions are depressed.An elevated 24-hour urine calcium concentration is consistent with the diagnosis but is not specific. Additionally, angiotensin-converting enzyme (ACE) activity is elevated in the serum in approximately two-thirds of patients with sarcoidosis. However, false-positive and false-negative results are common. Calcitriol as well as ACE could represent unregulated secretion products from granulomatous tissue, and their plasma concentrations may roughly reflect activity of the disease.

Response to corticosteroid therapy is often excellent, but in rare cases, the administration of cyclophosphamide may be of value when corticosteroids do not prove efficacious. Still, progressive interstitial fibrosis may result and these patients, a small subgroup of cases with nonresponding disease, may eventually develop CRF.

AMYLOIDOSIS

The amyloidoses constitute a group of diseases in which proteins deposit extracellularly in tissues as insoluble fibrils. Renal disease is a frequent manifestation of the systemic amyloidoses and often is the major source of morbidity for individuals with these disorders. Without treatment, amyloidosis-associated kidney disease usually progresses to end-stage renal disease (ESRD). Substantial progress in understanding the process of amyloid fibril formation and the mechanisms underlying disease manifestations have led to important advances in treatment, some of which have applicability not only to the amyloidoses but also to other protein-folding disorders and deposition diseases. Although this review focuses on amyloidosis-associated kidney disease, it is important to appreciate the impact of extrarenal disease on outcomes and treatment approaches.

Classification of the amyloidoses is based on the precursor protein that forms the amyloid fibrils and the distribution of amyloid deposition as either systemic or localized. The major types of systemic amyloidosis are Ig light chain (AL), Ig heavy chain (AH), amyloid A (AA), the familial or hereditary amyloidoses (TTR, fibrinogen Aα, lysozyme, apolipoprotein AI [apoAI], apoAII, gelsolin, and cystatin), senile systemic amyloidosis, and β2-microglobulin (β2m) amyloidosis. In AL amyloidosis, an immunoglobulin (Ig) light chain or light-chain fragment produced by clonal plasma cells deposits in tissue as amyloid. Any organ except the central nervous system can be a site of AL amyloid deposition, and the kidney is affected in 50 to 80 % of individuals.

Histologic Demonstration of Amyloid

The diagnosis of amyloidosis requires histologic demonstration of amyloid deposits. This usually is

accomplished by staining with Congo red dye. Congo red–stained amyloid has an orange-red appearance under light microscopy and produces apple-green birefringence under polarized light. The birefringence results from the ordered intercalation of Congo red dye into the amyloid fibrils, and this optical property must be present to consider the staining Congo red positive. Congo red staining can be technically difficult, particularly if tissue sections are <5 μm in thickness. Overstaining the tissue is an additional potential problem and can produce false-positive results. Thioflavin T, another molecule that binds to amyloid fibrils, is used less frequently than Congo red. Binding of thioflavin T to amyloid produces yellow-green fluorescence.

Any tissue can be evaluated for Congo red positivity, and the yield is greatest from sites with clinical evidence of involvement. However, if amyloidosis is suspected, the diagnosis often can be confirmed with abdominal fat aspiration rather than an invasive biopsy. The sensitivity of Congo red staining of abdominal fat is approximately 80 to 90 % and 65 to 75 % in AL and AA amyloidosis, respectively, but substantially lower in many of the familial amyloidoses. Therefore, the absence of Congo red positivity of abdominal fat does not eliminate the diagnosis. Salivary gland and rectal biopsies also are used as relatively noninvasive methods for demonstrating amyloid in tissue.

Because Congo red staining is not a routine part of the histologic evaluation of most tissues, the diagnosis of amyloidosis frequently is missed unless the disease is suspected. The likelihood of a missed diagnosis is lower with a kidney biopsy than with biopsies of other tissues because amyloid fibrils are visible by electron microscopy, a standard component of the histologic examination of kidney. The presence of characteristic fibrils by electron microscopy should trigger confirmatory staining of the tissue with Congo red dye.

However, even when electron microscopy is performed, the diagnosis of amyloidosis can be missed if fibrils are scant. Such cases sometimes are misdiagnosed as minimal-change disease.

Determination of the Type of Amyloidosis

Different types of amyloid are indistinguishable by light or electron microscopy. The most direct method for identifying the amyloidogenic protein is by mass spectrometry or amino acid sequencing of proteins that are extracted from amyloid deposits. These techniques are not available routinely and usually are not necessary unless other approaches are unrevealing. The most definitive method used in the clinical setting is immunofluorescence or immunohistochemical staining of tissue using antibodies that are directed against known amyloidogenic proteins. However, less direct methods often are required because of lack of sensitivity or availability of antibody reagents.

In the absence of immunoreactivity of tissue amyloid for λ or κ light chain, evidence for AL disease, the most common type of amyloidosis, is provided by demonstration of a monoclonal Ig protein in the blood or urine or clonal plasma cells in the bone marrow. Because the quantity of the circulating monoclonal protein is lower in AL amyloidosis than in multiple myeloma, immunofixation electrophoresis rather than simple protein electrophoresis often is required for detection of the monoclonal protein. Nephelometric quantification of free light chains in serum is useful in establishing the presence of a monoclonal protein as well as in following disease progression or response to treatment. It is important to recognize that in the setting of renal impairment, it is the ratio of the serum concentrations of the two light-chain isotypes rather than the absolute serum concentrations that is relevant, because free light chains are filtered by the kidney.

In addition to its use in assessing plasma cell clonality, a bone marrow biopsy is important for determining the plasma cell burden. The percentage of plasma cells usually is normal or only slightly increased in AL amyloidosis unless the disease occurs in conjunction with multiple myeloma. Because of the frequency of clinically unimportant monoclonal gammopathies in elderly patients, the presence of a monoclonal gammopathy should not lead to the conclusion that the amyloid is of the light-chain variety unless there is immunohistochemical evidence of light chains in the amyloid deposits or there has been a thorough evaluation for other types of amyloidosis.

AA disease usually is suspected when amyloidosis occurs in the setting of an inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, FMF or other periodic fever syndromes, bronchiectasis, or chronic osteomyelitis. The underlying disease usually is longstanding, and active inflammation typically is present when amyloidosis becomes evident. Some of the predisposing diseases, such as rheumatoid arthritis, are very prevalent in the adult population; therefore, immunohistochemical demonstration of AA protein in tissue amyloid or a careful evaluation for other types of amyloidosis should be performed before concluding that the type of amyloidosis is AA.

Renal Pathology

Because the kidney frequently is affected in AL, AA, and several of the familial amyloidoses, a kidney biopsy often is the method by which the disease is identified. Concern sometimes is raised about the risk for procedure-related bleeding as a result of vascular fragility in individuals with amyloidosis; however, there is little evidence that rates of bleeding after kidney biopsy actually are higher in these patients. Amyloid can be found anywhere in the kidney, but glomerular deposition typically predominates. By light

microscopy, glomerular amyloid appears as amorphous material in the mesangium and capillary loops. Substantial mesangial deposition can produce nodules that resemble lesions of diabetic nephropathy or light-chain deposition disease (LCDD). However, in amyloidosis, because the nodules are composed of amyloid protein rather than extracellular matrix, periodic acid-Schiff (PAS) staining is weak. Amyloid deposition in the tubulointerstitium produces tubular atrophy and interstitial fibrosis, and in a small proportion of patients, glomerular deposition is scant or absent and the amyloid is confined to the tubulointerstitium or vasculature. Irrespective of the distribution of amyloid, Congo red staining produces the disease-defining birefringence under polarized light.

Immunofluorescence or immunohistochemical studies are negative for intact Ig, complement, and fibrin but, in AL disease, often will reveal Ig light chain. Because the amyloidogenic light chain is produced by clonal plasma cells, reactivity should be restricted to a single light chain isotype, although there often is some degree of background staining for light chains in general, as well as for albumin. In contrast to multiple myeloma, the monoclonal protein in AL amyloidosis more often is of the λ than the κ isotype. It is important to be aware that the absence of reactivity for either λ or κ light chain does not rule out AL disease. Commercially available reagents do not always detect amyloidogenic light chains because of conformational change or fragmentation that masks or eliminates the relevant epitopes. In contrast, AA amyloid usually is detected with available antibodies against AA protein. Loss of Congo red staining after treatment with potassium permanganate is a property of AA amyloid that can distinguish it from other types, but this technique is not as reliable as immunoreactivity with anti-AA antibodies that currently are available.

Clinicopathologic Correlates

Proteinuria is present in the majority of individuals with renal amyloidosis and ranges from subnephrotic to massive with urinary protein excretion rates as high as 20 to 30 g/d. The urinary protein is composed mostly of albumin, and the proteinuria usually is accompanied by other components of the nephrotic syndrome. Hypoalbuminemia can be profound, and edema often is severe and refractory to diuretics. The multisystem nature of systemic amyloidosis can contribute to the difficulty of managing fluid retention, particularly in AL amyloidosis, since cardiac and autonomic nervous system involvement can cause hemodynamic fragility that limits the effectiveness or tolerability of diuretics. When amyloid is confined to the tubulointerstitium or vasculature, proteinuria is minimal and reduced GFR is the principal clinical manifestation. Renal impairment tends to progress less rapidly when tubulointerstitial rather than glomerular deposition predominates. Vascular involvement often is accompanied by hypertension, an otherwise uncommon feature of amyloidosis.

An unusual but well-documented manifestation of renal amyloidosis is nephrogenic diabetes insipidus caused by amyloid deposition in the peri-collecting duct tissue. In fact, early evidence for the role of the collecting ducts in the urinary concentrating mechanism of the kidneys was provided by postmortem dissection of the kidneys from a patient with amyloidosis and vasopressin-unresponsive diabetes insipidus. The amyloid deposits in that patient were confined almost exclusively to the tissue surrounding the medullary collecting ducts. Another extraglomerular manifestation of renal amyloidosis is Fanconi's syndrome, reflecting injury to proximal tubular cells by filtered light chains. Amyloid deposits that are isolated to the renal medulla is a feature in most patients with apoAI familial amyloidosis and has been described in some individuals with AA amyloidosis.

Medullary-limited disease can elude pathologic diagnosis if the biopsy specimen consists only of renal cortex.

Like other infiltrative diseases, amyloidosis can cause enlargement of the kidneys. However, in most patients, the kidneys seem to be of normal size by imaging studies, and the absence of enlarged kidneys should not decrease suspicion for the disease during diagnostic evaluation.

Clear relationships between the extent of amyloid deposition evident by kidney biopsy and severity of clinical manifestations have not been demonstrated. Urinary protein excretion or rate of GFR decline cannot be predicted on the basis of biopsy findings. Whether this lack of clinicopathologic correlation reflects sampling bias or pathogenic mechanisms is not clear.

Pathogenesis of Renal Amyloidosis

Two mechanisms of organ dysfunction in amyloidosis: The right side depicts the traditional view that amyloid fibrils accumulate in the extracellular space, causing physical disruption and malfunction of surrounding tissue. The left side depicts an alternative mechanism of direct cellular toxicity by amyloidogenic precursor proteins, folding intermediates, aggregates, or fibrils. This toxicity may be mediated through interactions with cell surface receptors or *via* entry into cells (Figure 2).

In amyloidosis-associated renal disease, indirect support for a role of the amyloidogenic precursors in disease manifestations comes from several observations. Proteinuria decreases rapidly after treatment that eliminates or markedly reduces production of the amyloidogenic precursor protein. In AL disease, this observation has been made after high-dose chemotherapy that eliminates the clonal plasma cells that produce the monoclonal amyloidogenic light chain and in AA disease, when the underlying inflammatory disease becomes

quiescent. Similar to the proBNP response in cardiac amyloidosis, the reduction in proteinuria occurs in many patients before substantial degradation of existing amyloid deposits would be expected to occur. Indeed, in small series of patients with AL amyloidosis who underwent serial kidney biopsies, the extent of amyloid deposition seemed to be similar in biopsies that were performed before treatment and after treatment-induced resolution of proteinuria. A lack of biopsy improvement after proteinuria resolution in AA amyloidosis also has been reported. Also consistent with a functional effect of amyloidogenic precursor proteins are *in vitro* demonstrations of specific phenotypic changes in cultured mesangial cells that are exposed to amyloidogenic light chains, changes that are not seen when the cells are exposed to non-amyloidogenic light chains.

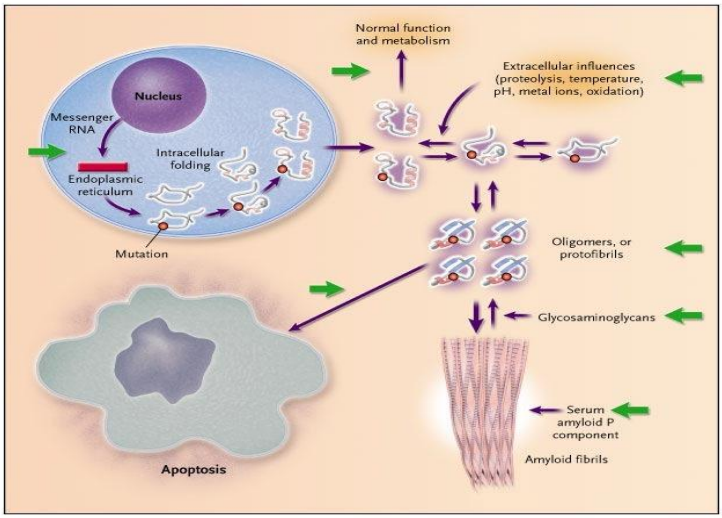

Figure 2 – Molecular Mechanisms of Amyloidosis

Treatment Approaches

Ongoing amyloid deposition in the kidney is associated with progressive deterioration in renal function. Overall, renal deterioration probably is most rapid in AL amyloidosis; however, the rate of progression varies considerably within all types of amyloidosis and probably reflects, at least to some extent, the rapidity of production of the amyloidogenic precursor protein. Hemodynamic alterations that result from severe nephrotic syndrome, autonomic dysfunction, or heart failure often underlie abrupt changes in kidney function and contribute to the fragility in renal function that frequently is present in this disease. The sections that follow review the treatment approaches for several types of amyloidosis with an emphasis on the impact of treatment on the kidney. Most of the detailed information about renal response to treatment comes from experience with AL amyloidosis.

AL Amyloidosis

The goal of current treatment approaches for AL amyloidosis is to eradicate the clonal plasma cells that produce the amyloidogenic light chain. The prognosis of AL amyloidosis has improved substantially during the past decade with the increasing use of aggressive anti-plasma cell treatment. Several chemotherapeutic regimens have been evaluated, and high-dose intravenous melphalan followed by autologous stem cell transplantation to support bone marrow recovery (HDM/SCT) has emerged as the most likely to eliminate the clonal plasma cells. Experience from several treatment centers has suggested that 25 to 50 % of patients who undergo such treatment have complete hematologic responses, meaning that there is no evidence of ongoing production of the monoclonal light chain. In contrast, complete hematologic responses are exceedingly rare with oral melphalan and

prednisone administered in repeated cycles, an approach that was standard treatment until relatively recently.

AA Amyloidosis

The current treatment approach for AA amyloidosis is to treat the underlying inflammatory disease and thereby reduce production of SAA. In FMF, a disease that is associated with a high rate of AA amyloidosis, life-long treatment with colchicine to inhibit FMF-associated inflammation prevents the development of amyloidosis in many patients. Once amyloidosis occurs, whether secondary to FMF or to other inflammatory diseases, suppression of inflammation can result in reduction in the clinical manifestations of amyloidosis and improved survival. Marked reductions in proteinuria have been reported in individuals with AA amyloidosis–associated kidney disease from a variety of underlying inflammatory conditions after treatment with cytotoxic agents or TNF antagonists. These functional improvements are presumed to be due to suppression of SAA production and resultant reduction in AA amyloid formation.

In many individuals with AA amyloidosis, adequate suppression of SAA production is not possible. Fibrillogenesis inhibition using small molecules that have structural similarity to glycosaminoglycan (GAG) moieties is an alternative treatment approach that is under investigation in AA amyloidosis as well as in Alzheimer's disease.

Regression of Amyloid Deposits

There is general consensus that amyloid deposits can regress over time *via* endogenous degradation. The rapidity of such degradation and the relationship between amyloid regression and functional improvements that occur after new amyloid production is halted are less clear. Scinitigraphy with

radiolabeled serum amyloid P (SAP), a protein that binds to all types of amyloid, is available in a limited number of centers as a noninvasive tool for monitoring disease status. Dramatic reductions in SAP uptake after treatments that eradicate amyloidogenic precursor proteins have been attributed to rapid regression of amyloid deposits.

Emerging Treatment Strategies

Tremendous advances have been made during the past several years in elucidating the structure and the chemistry of amyloid proteins, the mechanisms of fibril formation and tissue deposition, and the processes involved in tissue injury. This increased understanding has been accompanied by progress in developing novel treatment approaches that are directed not only at the source of the precursor protein but also at each of the steps in the pathway from precursor protein production to amyloid degradation. Small molecules that stabilize precursor proteins in their native conformation and thereby prevent generation of the misfolded variants have been identified. One such agent, the nonsteroidal anti-inflammatory drug diflunisal, maintains TTR as a homotetramer, a conformation that is thermodynamically more stable and thus less amyloidogenic than its monomeric counterpart. This strategy is being evaluated in a clinical trial for hereditary TTR amyloidosis. The use of small sulfonated molecules that are designed to interfere with interactions between amyloid proteins and GAGs targets both amyloid fibril formation and tissue deposition. Fibrillogenesis also is being targeted with synthetic peptides that inhibit aggregation and with antibodies that are directed against amyloid fibrils. Enhancing amyloid mobilization from tissue by targeting components of amyloid deposits that protect fibrils from proteolysis is yet another strategy under development.

ACUTE RENAL FAILURE

Acute renal failure (ARF) is characterized by a rapid decline in glomerular filtration rate (GFR) over hours to days. Depending on the exact definition used, ARF complicates approximately 5–7 % of hospital admissions and up to 30 % of admissions to intensive care units. Retention of nitrogenous waste products, oliguria (urine output <400 mL/d contributing to extracellular fluid overload), and electrolyte and acid-base abnormalities are frequent clinical features. ARF is usually asymptomatic and diagnosed when biochemical monitoring of hospitalized patients reveals a new increase in blood urea and serum creatinine concentrations.

Causes of ARF are generally divided into three major categories:

1) diseases that cause renal hypoperfusion, resulting in decreased function without frank parenchymal damage (*prerenal ARF*, or azotemia) (~55 %);

2) diseases that directly involve the renal parenchyma (*intrinsic ARF*) (~40 %);

3) diseases associated with urinary tract obstruction (*postrenal ARF*) (~5 %).

ARF is often considered to be reversible, although a return to baseline serum creatinine concentrations postinjury might not be sufficiently sensitive to detect clinically significant irreversible damage that may ultimately contribute to chronic kidney disease. ARF is associated with significant in-hospital morbidity and mortality, the latter in the range of 30–60 %, depending on the clinical setting and presence or absence of nonrenal organ system failure.

Etiology and Pathophysiology

Prerenal ARF (Prerenal Azotemia). The most common

form of ARF is prerenal ARF, which occurs in the setting of renal hypoperfusion. Prerenal ARF is generally reversible when renal perfusion pressure is restored. By definition, renal parenchymal tissue is not damaged. More severe or prolonged hypoperfusion may lead to ischemic injury, often termed *acute tubular necrosis*, or ATN. Thus, prerenal ARF and ischemic ATN fall along a spectrum of manifestations of renal hypoperfusion. As shown in Table 1, prerenal ARF can complicate any disease that induces hypovolemia, low cardiac output, systemic vasodilatation, or selective intrarenal vasoconstriction.

Table 4 - Classification and Major Causes of Acute Renal Failure

Prerenal ARF
1 Hypovolemia
A Increased extracellular fluid losses: hemorrhage
B Gastrointestinal fluid loss: vomiting, diarrhea, enterocutaneous fistula
C Renal fluid loss: diuretics, osmotic diuresis, hypoadrenalism, nephrogenic diabetes insipidus
D Extravascular sequestration: burns, pancreatitis, severe hypoalbuminemia (hypoproteinemia)
E Decreased intake: dehydration, altered mental status
2 Altered renal hemodynamics resulting in hypoperfusion
A Low cardiac output state: diseases of the myocardium, valves, and pericardium (including tamponade); pulmonary hypertension or massive pulmonary embolism leading to right and left heart failure; impaired venous return (e.g., abdominal compartment syndrome or positive pressure ventilation)

Continuation of Table 4

B Systemic vasodilation: sepsis, antihypertensives, afterload reducers, anaphylaxis
C Renal vasoconstriction: hypercalcemia, catecholamines, calcineurin inhibitors, amphotericin B
D Impairment of renal autoregulatory responses: cyclooxygenase inhibitors (e.g., nonsteroidal anti-inflammatory drugs), angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers
E Hepatorenal syndrome
Intrinsic ARF
1 Renovascular obstruction (bilateral, or unilateral in the setting of one kidney)
A Renal artery obstruction: atherosclerotic plaque, thrombosis, embolism, dissection aneurysm, large vessel vasculitis
B Renal vein obstruction: thrombosis or compression
2 Diseases of the glomeruli or vasculature
A Glomerulonephritis or vasculitis
B. Other: thrombotic microangiopathy, malignant hypertension, collagen vascular diseases (systemic lupus erythematosus, scleroderma), disseminated intravascular coagulation, preeclampsia
3 Acute tubular necrosis
A Ischemia: causes are the same as for prerenal ARF, but generally the insult is more severe and/or more prolonged
B Infection, with or without sepsis syndrome

Continuation of Table 4

C Toxins:
1) Exogenous: radiocontrast, calcineurin inhibitors, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), antifungals (e.g., amphotericin B), ethylene glycol
2) Endogenous: rhabdomyolysis, hemolysis
4 Interstitial nephritis
A Allergic: antibiotics (lactams, sulfonamides, quinolones, rifampin), nonsteroidal anti-inflammatory drugs, diuretics, other drugs
B Infection: pyelonephritis (if bilateral)
C Infiltration: lymphoma, leukemia, sarcoidosis
D Inflammatory, nonvascular: Sjögren's syndrome, tubulointerstitial nephritis with uveitis
5 Intratubular obstruction
A Endogenous: myeloma proteins, uric acid (tumor lysis syndrome), systemic oxalalosis
B Exogenous: acyclovir, gancyclovir, methotrexate, indinavir
Postrenal ARF (Obstruction)
1 Ureteric (bilateral, or unilateral in the case of one kidney): calculi, blood clots, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
2 Bladder neck: neurogenic bladder, prostatic hypertrophy, calculi, blood clots, cancer
3 Urethra: stricture or congenital valves

Hypovolemia leads to a fall in mean systemic arterial pressure, which is detected as reduced stretch by arterial (e.g.,

carotid sinus) and cardiac baroreceptors. In turn, this triggers a coordinated series of neurohormonal responses that aim to restore blood volume and arterial pressure. These include activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, as well as release of arginine vasopressin. Relatively "nonessential" vascular beds (such as the musculocutaneous and splanchnic circulations) undergo vasoconstriction in an attempt to preserve cardiac and cerebral perfusion pressure. In addition, salt loss through sweat glands is inhibited, and thirst and salt appetite are stimulated. Renal salt and water retention also occur.

In states of mild hypoperfusion, glomerular perfusion and the filtration fraction are preserved through several compensatory mechanisms. In response to the reduction in perfusion pressure, stretch receptors in afferent arterioles trigger afferent arteriolar vasodilatation through a local myogenic reflex (autoregulation). Angiotensin II increases biosynthesis of vasodilator prostaglandins (e.g., prostaglandin E_2 and prostacyclin), also resulting in afferent arteriolar vasodilation. In addition, angiotensin II induces preferential constriction of efferent arterioles. As a result, the fraction of plasma flowing through glomerular capillaries that is filtered is increased (filtration fraction), intraglomerular pressure is maintained, and GFR is preserved. With more severe hypoperfusion, these compensatory responses are overwhelmed and GFR falls, leading to prerenal ARF.

Autoregulatory dilatation of afferent arterioles allows for maintenance of GFR despite systemic hypotension; however, when hypotension is severe or prolonged, these autoregulatory mechanisms fail, resulting in a precipitous decline in GFR. Lesser degrees of hypotension may provoke prerenal ARF in those at risk: the elderly and patients with diseases that affect the integrity of afferent arterioles (e.g., hypertensive nephrosclerosis, diabetic vasculopathy and other

forms of occlusive (including atherosclerotic) renovascular disease). In addition, drugs that interfere with adaptive responses to hypoperfusion may convert compensated renal hypoperfusion into overt prerenal ARF or ATN. Pharmacologic inhibitors of renal prostaglandin biosynthesis [nonsteroidal anti-inflammatory drugs (NSAIDs)] or angiotensin-converting enzyme (ACE) activity (ACE inhibitors) and angiotensin II receptor blockers (ARBs) are major culprits. While NSAIDs do not compromise GFR in healthy individuals, these medications may precipitate prerenal ARF in patients with volume depletion or in those with chronic kidney disease (in whom GFR is maintained, in part, through prostaglandin-mediated hyperfiltration by the remaining functional nephrons). ACE inhibitors should be used with special care in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney. In these settings, glomerular perfusion and filtration may be exquisitely dependent on the actions of angiotensin II. Angiotensin II preserves GFR in these circumstances by raising systemic arterial pressure and by triggering selective constriction of efferent arterioles. ACE inhibitors and ARBs blunt these responses and can precipitate ARF.

Hepatorenal Syndrome. Hepatorenal syndrome (HRS) is a unique form of prerenal ARF that frequently complicates advanced cirrhosis as well as acute liver failure. In HRS the kidneys are structurally normal but fail due to splanchnic vasodilation and arteriovenous shunting, resulting in profound renal vasoconstriction. Correction of the underlying liver disease (e.g., by liver transplantation) results in resolution of the acute renal failure. There are two forms of HRS, type 1 and type 2, that differ in their clinical course. In type I HRS, the more aggressive form of the disease, ARF progresses even after optimization of systemic hemodynamics and carries a mortality rate of >90 %.

Intrinsic ARF. Intrinsic causes of ARF can be conceptually divided based on the predominant compartment of the kidney that is affected: (1) ischemic or nephrotoxic tubular injury, (2) tubulointerstitial diseases, (3) diseases of the renal microcirculation and glomeruli, and (4) diseases of larger renal vessels. Ischemia and nephrotoxins classically induce acute tubular injury. Although many patients with ischemic or nephrotoxic ARF do not have morphologic evidence of cellular necrosis, this disease is often referred to as *acute tubular necrosis*, or ATN. More recently, because of the important role of sublethal injury to tubular epithelial and other renal cells (e.g., endothelial cells) in the pathogenesis of this syndrome, the term *acute kidney injury* (AKI) has been proposed.

Etiology and Pathophysiology of Ischemic ATN. Prerenal ARF and ischemic ATN are part of a spectrum of manifestations of renal hypoperfusion. In its most extreme form, ischemia leads to bilateral renal cortical necrosis and irreversible renal failure. ATN differs from prerenal ARF in that the renal tubular epithelial cells are injured in the latter. ATN occurs most frequently in patients undergoing major cardiovascular surgery or suffering severe trauma, hemorrhage, sepsis, and/or volume depletion. Patients with other risk factors for ARF (e.g., exposure to nephrotoxins or preexisting chronic kidney disease) are at increased risk for ATN. Recovery typically takes 1–2 weeks after normalization of renal perfusion, as it requires repair and regeneration of renal cells.

The course of ischemic ATN is typically characterized by four phases: initiation, extension, maintenance, and recovery. These phases are often preceded by a period of prerenal azotemia. During the *initiation phase* (lasting hours to days), GFR declines because (1) glomerular ultrafiltration pressure is reduced as renal blood flow falls, (2) the flow of filtrate within tubules is obstructed by casts comprised of shed

epithelial cells and necrotic debris, and (3) there is backleak of glomerular filtrate through injured tubular epithelium. Ischemic injury is most prominent in the S_3 segment of the proximal tubule and the medullary portion of the thick ascending limb of the loop of Henle. These segments of the tubule are particularly sensitive to ischemia because of high rates of active (ATP-dependent) solute transport and location in the outer medulla, where the partial pressure of oxygen is low, even under basal conditions. Cellular ischemia results in ATP depletion, inhibition of active sodium transport, cytoskeletal disruption, loss of cell polarity, cell-cell and cell-matrix attachment, and oxygen free-radical formation. Renal injury may be limited by restoration of renal blood flow during this period. If severe, cell injury results in apoptosis or necrosis.

The *extension phase* follows the initiation phase and is characterized by continued ischemic injury and inflammation. It has been proposed that endothelial damage (resulting in vascular congestion) contributes to both of these processes. During the *maintenance phase* (typically 1–2 weeks), GFR stabilizes at its nadir (typically 5–10 mL/min), urine output is lowest, and uremic complications may arise. It is not clear why the GFR remains low during this phase, despite correction of systemic hemodynamics. Proposed mechanisms include persistent intrarenal vasoconstriction and medullary ischemia triggered by dysregulated release of vasoactive mediators from injured endothelial cells, congestion of medullary blood vessels, and reperfusion injury induced by reactive oxygen species and inflammatory mediators released by leukocytes or renal parenchymal cells. In addition, epithelial cell injury may contribute to persistent intrarenal vasoconstriction through *tubuloglomerular feedback.* Specialized epithelial cells in the macula densa region of distal tubules detect increases in distal salt delivery that occur as a consequence of impaired reabsorption by more proximal nephron segments. Macula

densa cells, in turn, stimulate constriction of adjacent afferent arterioles by a poorly defined mechanism and further compromise glomerular perfusion and filtration, thereby contributing to a vicious circle.

The *recovery phase* is characterized by tubular epithelial cell repair and regeneration as well as a gradual return of GFR toward premorbid levels. The recovery phase may be complicated by a marked diuretic phase due to delayed recovery of epithelial cell function (solute and water reabsorption) relative to glomerular filtration.

Etiology and Pathophysiology of Nephrotoxic ARF. Nephrotoxic ATN may complicate exposure to many structurally diverse pharmacologic agents. With most nephrotoxins, the incidence of ARF is increased in the elderly and in patients with preexisting chronic kidney disease, true or "effective" hypovolemia, or concomitant exposure to other toxins.

Radiocontrast agents, cyclosporine, and tacrolimus (FK506) cause kidney injury through intrarenal vasoconstriction. Consequently, ATN in association with these medications is characterized by an acute fall in renal blood flow and GFR, relatively benign urine sediment, and a low fractional excretion of sodium (see below). Severe cases may show clinical or pathologic evidence of tubular cell necrosis. Contrast nephropathy is also thought to result from the generation of reactive oxygen species that are directly toxic to renal tubular epithelial cells. Contrast nephropathy classically presents as an acute (onset within 24–48 h) but reversible (peak 3–5 days, resolution within 1 week) rise in blood urea nitrogen and serum creatinine. Contrast nephropathy is most common in individuals with preexisting chronic kidney disease, diabetes mellitus, congestive heart failure, hypovolemia, or multiple myeloma. The type (low vs. isoosmolar contrast) and dose of

contrast also influence the likelihood of injury associated with its administration.

Antibiotics and anticancer drugs typically cause ATN through direct toxicity to the tubular epithelial cells and/or intratubular obstruction. ARF complicates 10–30 % of courses of *aminoglycoside antibiotics*. Aminoglycosides accumulate in renal tubular epithelial cells, where they cause oxidative stress and cell injury; thus, ARF usually occurs after several days of aminoglycoside therapy. Damage may occur in both the proximal and distal tubule; defects in the distal tubule may result in decreased concentrating ability. *Amphotericin B* causes dose-related ARF through intrarenal vasoconstriction and direct toxicity to proximal tubule epithelium. Newer (liposomal) formulations of amphotericin B may be associated with less nephrotoxicity. Acyclovir may precipitate in the renal tubules and cause acute renal failure. Foscarnet and pentamidine are less commonly prescribed antimicrobials also frequently associated with acute renal failure. Cisplatin and carboplatin, like the aminoglycosides, are accumulated by proximal tubule cells and typically provoke ARF after 7–10 days of exposure, typically in association with potassium and magnesium wasting. Ifosphamide administration may lead to hemorrhagic cystitis, manifested by hematuria, as well as acute and chronic renal failure. Type II renal tubular acidosis (Fanconi syndrome) often accompanies ifosphamide-associated ARF.

Endogenous nephrotoxins include calcium, myoglobin, hemoglobin, urate, oxalate, and myeloma light chains. Hypercalcemia can compromise GFR, predominantly by inducing intrarenal vasoconstriction as well as volume depletion from obligate water loss. Both *rhabdomyolysis* and *hemolysis* can induce ARF. Common causes of rhabdomyolysis include traumatic crush injury, acute muscle ischemia, prolonged seizure activity, excessive exercise, heat stroke or

malignant hyperthermia, and infectious or metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism). ARF due to hemolysis is relatively rare and is observed following blood transfusion reactions. It has been postulated that myoglobin and hemoglobin promote intrarenal oxidative stress, resulting in injury to tubular epithelial cells and inducing intratubular cast formation. In addition, cell-free hemoglobin and myoglobin are potent inhibitors of nitric oxide bioactivity and may trigger intrarenal vasoconstriction and ischemia. Hypovolemia or acidosis may further promote intratubular cast formation. Intratubular casts containing filtered immunoglobulin light chains and other proteins (including Tamm-Horsfall protein produced by thick ascending limb cells) cause ARF in patients with *multiple myeloma* (myeloma cast nephropathy). Light chains are also directly toxic to tubule epithelial cells. Intratubular obstruction is an important cause of ARF in patients with severe *hyperuricosuria* or *hyperoxaluria*. Acute uric acid nephropathy can complicate the treatment of selected lymphoproliferative or myeloproliferative disorders (e.g., Burkitt's lymphoma, acute myelogenous leukemia), especially after the administration of chemotherapy, resulting in increased cell lysis ("tumor lysis syndrome").

Pathology of Ischemic and Nephrotoxic ATN. The classic pathologic features of ischemic ATN are patchy and focal necrosis of the tubular epithelium, with detachment of cells from the basement membrane, and occlusion of tubule lumens with casts composed of intact or degenerating epithelial cells, Tamm-Horsfall protein, and pigments. Leukocyte accumulation is frequently observed in vasa recta; however, the morphology of the glomeruli and renal vasculature is characteristically normal. Necrosis is most severe in the S3 segment of proximal tubules but may also affect the medullary thick ascending limb of the loop of Henle.

With exposure to nephrotoxins, morphologic changes tend to be most prominent in both the convoluted and straight portions of proximal tubules. Cellular necrosis is less pronounced than in ischemic ATN.

Other Causes of Intrinsic ARF. Virtually any pharmacologic agent may trigger allergic interstitial nephritis, which is characterized by infiltration of the tubulointerstitium by granulocytes (typically but not invariably eosinophils), macrophages, and/or lymphocytes and by interstitial edema. The most common offenders are antibiotics (e.g., penicillins, cephalosporins, quinolones, sulfonamides, rifampin) and NSAIDs.

Patients with advanced atherosclerosis can develop ARF after manipulation of the aorta or renal arteries during surgery or angiography, following trauma, or, rarely, spontaneously (atheroembolic ARF).

Postrenal ARF. Urinary tract obstruction accounts for fewer than 5 % of cases of hospital-acquired ARF. Because one kidney has sufficient reserve to handle generated nitrogenous waste products, ARF from obstruction requires obstruction to urine flow between the external urethral meatus and bladder neck, bilateral ureteric obstruction, or unilateral ureteric obstruction in a patient with one functioning kidney or with significant preexisting chronic kidney disease. Bladder neck obstruction is the most common cause of postrenal ARF and is usually due to prostatic disease (e.g., hypertrophy, neoplasia, or infection), neurogenic bladder, or therapy with anticholinergic drugs. Less common causes of acute lower urinary tract obstruction include blood clots, calculi, and urethritis with spasm. Ureteric obstruction may result from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia),

or external compression (e.g., retroperitoneal fibrosis, neoplasia or abscess, inadvertent surgical ligature). During the early stages of obstruction (hours to days), continued glomerular filtration leads to increased intraluminal pressure upstream to the site of obstruction. As a result, there is gradual distention of the proximal ureter, renal pelvis, and calyces and a fall in GFR.

Clinical Assessment

Symptoms of *prerenal* ARF include thirst and orthostatic dizziness. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor and dry mucous membranes suggest prerenal ARF. Careful clinical examination may reveal stigmata of chronic liver disease and portal hypertension, advanced cardiac failure, sepsis, or other causes of reduced "effective" arterial blood volume. Case records should be reviewed for documentation of a progressive fall in urine output and body weight and recent initiation of treatment with diuretics, NSAIDs, ACE inhibitors, or ARBs.

Hypovolemia, septic shock, and major surgery are important risk factors for ischemic ATN. The risk of ischemic ATN is increased further if ARF persists despite normalization of systemic hemodynamics. Diagnosis of nephrotoxic ATN requires careful review of the clinical data and records for evidence of recent exposure to nephrotoxic medications, radiocontrast agents, or endogenous toxins.

Although ischemic and nephrotoxic ATN account for >90 % of cases of intrinsic ARF, other renal parenchymal diseases must be considered. Fever, arthralgias, and a pruritic erythematous rash following exposure to a new drug suggest allergic interstitial nephritis, although systemic features of hypersensitivity are frequently absent. Flank pain may be a prominent symptom following occlusion of a renal artery or

vein and with other parenchymal diseases distending the renal capsule (e.g., severe glomerulonephritis or pyelonephritis). Subcutaneous nodules, livedo reticularis, bright orange retinal arteriolar plaques, and digital ischemia (“purple toes”), despite palpable pedal pulses, suggest atheroembolization. ARF in association with oliguria, edema, and hypertension, with an "active" urine sediment (nephritic syndrome), suggests acute glomerulonephritis or vasculitis. Malignant hypertension may result in ARF, often in association with hypertensive injury to other organs (e.g., papilledema, neurologic dysfunction, left ventricular hypertrophy) and may mimic glomerulonephritis in its other clinical manifestations.

Postrenal ARF may present with suprapubic and flank pain due to distention of the bladder and of the renal collecting system and capsule, respectively. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Prostatic disease is likely if there is a history of nocturia, frequency, and hesitancy and enlargement of the prostate on rectal examination. Neurogenic bladder should be suspected in patients receiving anticholinergic medications or with physical evidence of autonomic dysfunction. Definitive diagnosis of postrenal ARF hinges on judicious use of radiologic investigations and rapid improvement in renal function following relief of obstruction.

Urinalysis. Anuria suggests complete urinary tract obstruction but may complicate severe cases of prerenal or intrinsic renal ARF. Wide fluctuations in urine output raise the possibility of intermittent obstruction, whereas patients with partial urinary tract obstruction may present with polyuria due to impairment of urine concentrating mechanisms.

In prerenal ARF, the sediment is characteristically acellular and contains transparent hyaline casts (“bland”, “benign”, “inactive” urine sediment). Hyaline casts are formed in concentrated urine from normal constituents of urine -

principally Tamm-Horsfall protein, which is secreted by epithelial cells of the loop of Henle. Postrenal ARF may also present with inactive sediment, although hematuria and pyuria are common in patients with intraluminal obstruction or prostatic disease. Pigmented "muddy brown" granular casts and casts containing tubule epithelial cells are characteristic of ATN and suggest an ischemic or nephrotoxic etiology. These casts are usually found in association with mild “tubular” proteinuria (<1 g/d), reflecting impaired reabsorption and processing of filtered proteins by injured proximal tubules. Casts may be absent in 20–30% of patients with ATN and are not required for diagnosis. In general, red blood cell casts indicate glomerular injury or, less often, acute tubulointerstitial nephritis. White cell casts and nonpigmented granular casts suggest interstitial nephritis, whereas broad granular casts are characteristic of chronic kidney disease and probably reflect interstitial fibrosis and dilatation of tubules. Eosinophiluria (>5 % of urine leukocytes) is a common finding (~90 %) in antibiotic-induced allergic interstitial nephritis and can be detected with Hansel's stain; however, lymphocytes may predominate in allergic interstitial nephritis induced by NSAIDs and some other drugs (i.e. ampicillin, rifampicin, and interferon). Occasional uric acid crystals (pleomorphic in shape) are common in the concentrated urine of prerenal ARF but suggest acute urate nephropathy if seen in abundance. Oxalate (envelope-shaped) and hippurate (needle-shaped) crystals raise the possibility of ethylene glycol ingestion and toxicity.

Proteinuria of >1 g/d suggests injury to the glomerular ultrafiltration barrier ("glomerular proteinuria") or excretion of myeloma light chains. The latter may not be detected by conventional dipstick analysis, and other tests may be needed (e.g., sulfosalicylic acid precipitation, immunoelectrophoresis). Hemoglobinuria or myoglobinuria should be suspected if urine

is strongly positive for heme by dipstick but contains few red cells, and if the supernatant of centrifuged urine is positive for free heme. Bilirubinuria may provide a clue to the presence of HRS.

Renal Failure Indices

Analysis of urine and blood biochemistry may be useful for distinguishing prerenal ARF from ischemic or nephrotoxic intrinsic renal ARF. The fractional excretion of sodium (FE_{Na}) is most useful in this regard. The FE_{Na} relates sodium clearance to creatinine clearance. Sodium is reabsorbed avidly from glomerular filtrate in patients with prerenal ARF, in an attempt to restore intravascular volume. The FE_{Na} tends to be high in ischemic ATN but is often low in patients with sepsis-induced, pigment-induced, and some forms of nephrotoxic ATN (e.g., contrast-associated). In contrast, creatinine is not reabsorbed in either setting. Consequently, patients with prerenal ARF typically have a FE_{Na} of <1.0 % (frequently <0.1 %). In patients with metabolic alkalosis, where there may be obligate losses of sodium in the urine to maintain electroneutrality, the fractional excretion of chloride (FE_{Cl}) may be more sensitive than the FE_{Na} in detecting prerenal azotemia. The *urine sodium concentration* is a less-sensitive index for distinguishing prerenal ARF from ischemic and nephrotoxic ARF as values overlap between groups. Similarly, indices of urinary concentrating ability such as urine specific gravity, urine osmolality, urine-to-plasma urea ratio, and blood urea-to-creatinine ratio are of limited value in differential diagnosis.

Many caveats apply when interpreting biochemical renal failure indices. The FE_{Na} may be >1.0 % in prerenal ARF if patients are receiving diuretics or with preexisting chronic kidney disease, certain salt-wasting syndromes, or adrenal insufficiency.

Laboratory Findings

Serial serum creatinine measurements can provide useful insights to the cause of ARF. Prerenal ARF is typified by fluctuating serum creatinine levels that parallel changes in hemodynamic status. Creatinine rises rapidly (within 24–48 h) in patients with ARF following renal ischemia, atheroembolization, and radiocontrast exposure. Peak serum creatinine concentrations are observed after 3–5 days with contrast nephropathy and return to baseline after 5–7 days. In contrast, serum creatinine concentrations typically peak later (7–10 days) in ATN and atheroembolic disease. The initial rise in serum creatinine is characteristically delayed until the second week of therapy with many tubular epithelial cell toxins (e.g., aminoglycosides, cisplatin) and is thought to reflect the need for accumulation of these agents within tubular epithelial cells to cause injury.

Hyperkalemia, hyperphosphatemia, hypocalcemia, and elevations in serum uric acid and creatine kinase (MM isoenzyme) levels at presentation suggest a diagnosis of rhabdomyolysis. Hyperuricemia [>890 mol/L (>15 mg/dL)] in association with hyperkalemia, hyperphosphatemia, and increased circulating levels of intracellular enzymes such as lactate dehydrogenase may indicate acute urate nephropathy and tumor lysis syndrome following cancer chemotherapy. A wide anion and osmolal gap [the latter calculated as the difference between the observed (measured) serum osmolality minus the expected osmolality calculated from serum sodium, glucose, and urea concentrations] indicate the presence of an unusual anion or osmole in the circulation (e.g., ingestion of ethylene glycol or methanol). Severe anemia in the absence of hemorrhage raises the possibility of hemolysis, multiple myeloma, or thrombotic microangiopathy. Systemic eosinophilia suggests allergic interstitial nephritis but is also a feature of atheroembolic disease and polyarteritis nodosa.

Radiologic Findings

Imaging of the urinary tract by ultrasonography is useful to exclude postrenal ARF. CT and MRI are alternative imaging modalities. Whereas pelvicalyceal dilatation is usual with urinary tract obstruction (98% sensitivity), dilatation may be absent immediately following obstruction or in patients with ureteric encasement (e.g., retroperitoneal fibrosis, neoplasia). Retrograde or anterograde pyelography are more definitive investigations in complex cases and provide precise localization of the site of obstruction. A plain film of the abdomen or unenhanced helical CT scan is a valuable initial screening technique in patients with suspected nephrolithiasis. Magnetic resonance angiography (MRA) is often used to assess patency of renal arteries and veins in patients with suspected vascular obstruction. Alternative methods include Doppler ultrasound (which is much more operator-dependent than MRA) and CT-based angiography. Catheter-based angiography may be required for definitive diagnosis and treatment.

Renal Biopsy

Biopsy is reserved for patients in whom prerenal and postrenal ARF have been excluded and the cause of intrinsic ARF is unclear. Renal biopsy is particularly useful when clinical assessment and laboratory investigations suggest diagnoses other than ischemic or nephrotoxic injury that may respond to disease-specific therapy. Examples include glomerulonephritis, vasculitis, and allergic interstitial nephritis.

Complications

ARF impairs renal excretion of sodium, potassium, and water and perturbs divalent cation homeostasis and urinary acidification mechanisms. As a result, ARF is frequently

complicated by intravascular volume overload, hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypermagnesemia, and metabolic acidosis. In addition, patients are unable to excrete nitrogenous waste products and are prone to develop the uremic syndrome. The speed of development and the severity of these complications reflect the degree of renal impairment and catabolic state of the patient.

Expansion of extracellular fluid volume is an inevitable consequence of diminished salt and water excretion in oliguric or anuric individuals. Whereas milder forms are characterized by weight gain, bibasilar lung rales, raised jugular venous pressure, and dependent edema, continued volume expansion may precipitate life-threatening pulmonary edema. Excessive administration of free water, either through ingestion and nasogastric administration or as hypotonic saline or isotonic dextrose solutions, can induce *hypoosmolality* and *hyponatremia*, which, if severe, lead to neurologic abnormalities, including seizures.

Hyperkalemia is a frequent complication of ARF. Coexistent metabolic acidosis may exacerbate hyperkalemia by promoting potassium efflux from cells. Hyperkalemia may be particularly severe, even at the time of diagnosis, in patients with rhabdomyolysis, hemolysis, and tumor lysis syndrome. Mild hyperkalemia (<6.0 mmol/L) is usually asymptomatic. Higher levels may trigger electrocardiographic abnormalities and/or arrhythmias.

ARF is typically complicated by *metabolic acidosis*, often with an increased anion gap. Acidosis can be particularly severe when endogenous production of hydrogen ions is increased by other mechanisms (e.g., diabetic or fasting ketoacidosis; lactic acidosis complicating generalized tissue hypoperfusion, liver disease, or sepsis; metabolism of ethylene glycol or methanol).

Hyperphosphatemia is an almost invariable

complication of ARF. Severe hyperphosphatemia may develop in highly catabolic patients or following rhabdomyolysis, hemolysis, or tissue ischemia. Metastatic deposition of calcium phosphate can lead to *hypocalcemia*, particularly with elevation of serum calcium (mg/dL) and phosphate (mg/dL) concentrations. Other factors that contribute to hypocalcemia include tissue resistance to the actions of parathyroid hormone and reduced levels of 1,25-dihydroxyvitamin D. Hypocalcemia is often asymptomatic but can cause perioral paresthesia, muscle cramps, seizures, altered mental status, prolongation of the QT interval and other nonspecific T-wave changes on electrocardiography.

Anemia develops rapidly in ARF and is usually multifactorial in origin. Contributing factors include impaired erythropoiesis, hemolysis, bleeding, hemodilution, and reduced red cell survival time. Prolongation of the *bleeding time* is also common. Common contributors to the bleeding diathesis include mild thrombocytopenia, platelet dysfunction, and/or clotting factor abnormalities (e.g., factor VIII dysfunction). *Infection* is a common and serious complication of ARF. It is unclear whether patients with ARF have a clinically significant defect in host immune responses or whether the high incidence of infection reflects repeated breaches of mucocutaneous barriers (e.g., intravenous cannulae, mechanical ventilation, and bladder catheterization). *Cardiopulmonary complications* of ARF include arrhythmias, pericarditis and pericardial effusion, and pulmonary edema.

Protracted periods of severe ARF are invariably associated with the development of the *uremic syndrome*.

A *vigorous diuresis* can occur during the recovery phase of ARF (see above), which may be inappropriate on occasion and lead to intravascular volume depletion. *Hypernatremia* can also complicate recovery if water losses via hypotonic urine are not replaced or if losses are inappropriately

replaced by relatively hypertonic saline solutions. *Hypokalemia*, *hypomagnesemia*, *hypophosphatemia*, and *hypocalcemia* are less common metabolic complications during this period but may develop in response to injury associated with selected drugs (e.g., ifosphamide may lead to Fanconi syndrome or type II renal tubular acidosis associated with hypokalemia, acidosis, hypophosphatemia, and glycosuria).

Treatment

Prevention. Because there are no specific therapies for ischemic or nephrotoxic ARF, prevention is of paramount importance. Many cases of ischemic ARF can be avoided by close attention to cardiovascular function and intravascular volume in high-risk patients, such as the elderly and those with preexisting chronic kidney disease. Indeed, aggressive restoration of intravascular volume has been shown to dramatically reduce the incidence of ischemic ARF after major surgery or trauma, burns, or cholera. The incidence of nephrotoxic ARF can be reduced by tailoring the administration (dose and frequency) of nephrotoxic drugs to body size and GFR. In this regard, it should be noted that serum creatinine is a relatively insensitive index of GFR and may overestimate GFR considerably in small or elderly patients. For purposes of drug dosing, it is advisable to estimate the GFR using the Cockcroft-Gault formula (which factors in age, sex, and weight) or the simplified Modification of Diet in Renal Disease (MDRD) equation (which factors in age, sex, weight, and race. Of note, these equations cannot be used to estimate GFR when creatinine is not at steady state (e.g., during evolving ARF). Adjusting drug dosage according to circulating drug levels also appears to limit renal injury in patients receiving aminoglycoside antibiotics, cyclosporine, or tacrolimus. Diuretics, NSAIDs, ACE inhibitors, ARBs, and

vasodilators should be used with caution in patients with suspected true or "effective" hypovolemia or renovascular disease as they may precipitate prerenal ARF or convert the latter to ischemic ARF. Allopurinol and forced alkaline diuresis are useful prophylactic measures in patients at high risk for acute urate nephropathy (e.g., cancer chemotherapy in hematologic malignancies) to limit uric acid generation and prevent precipitation of urate crystals in renal tubules. Rasburicase, a recombinant urate-oxidase enzyme, catalyzes enzymatic oxidation of uric acid into a soluble metabolite, allantoin. Forced alkaline diuresis may also prevent or attenuate ARF in patients receiving high-dose methotrexate or suffering from rhabdomyolysis. *N*-acetylcysteine limits acetaminophen-induced renal injury if given within 24 h of ingestion.

A number of preventive measures have been proposed for contrast nephropathy. It is clear that hydration is an effective preventive measure. Other measures that have been proposed include loop diuretics and mannitol, dopamine, fenoldopam, *N*-acetylcysteine, theophylline, and sodium bicarbonate. Despite favorable experimental data, there is insufficient evidence to support the use of loop diuretics or mannitol to prevent radiocontrast nephropathy or any other cause of ARF. Likewise, despite its widespread use, dopamine has proved ineffective as a prophylactic agent. Fenoldopam, a dopamine a-1 specific agonist approved for use as a parenteral antihypertensive agent, has been tested in several clinical trials and does not appear to reduce the incidence of contrast nephropathy. Moreover, fenoldopam is associated with significant side effects, including systemic hypotension, and its use as an agent to prevent radiocontrast nephropathy should be discouraged. In contrast, several (relatively small) randomized clinical trials (RCTs) have suggested a clinical benefit to the use of *N*-acetylcysteine, although meta-analyses have been

inconclusive. However, aside from the potential hazards associated with a delay in radiographic imaging, *N*-acetylcysteine appears to be safe, and its use in patients at high risk for radiocontrast nephropathy is reasonable, based on its low side effect profile. Larger RCTs will be required to show definitive benefit. Theophylline and aminophylline (adenosine antagonists) offer the potential advantage of use immediately preceding radiocontrast administration, although the benefit, if present, appears marginal in most studies. Lastly, volume expansion with bicarbonate-containing intravenous fluids has been suggested to be superior to sodium chloride (saline) administration and showed a significant benefit in a single center RCT. Unlike *N*-acetylcysteine, the use of sodium bicarbonate does not obligate a delay in imaging (the published protocol began IV fluids 1 h before the imaging study was begun). Whether a combination of strategies (e.g., *N*-acetylcysteine + sodium bicarbonate) offers additive benefit and that patients require treatment remain unclear and warrant further study.

Specific Therapies

By definition, prerenal ARF is rapidly reversible upon correction of the primary hemodynamic abnormality, and postrenal ARF resolves upon relief of obstruction. To date there are no specific therapies for established AKI. Management of these disorders should focus on elimination of the causative hemodynamic abnormality or toxin, avoidance of additional insults, and prevention and treatment of complications. Specific treatment of other causes of intrinsic renal ARF depends on the underlying pathology.

Prerenal ARF. The composition of replacement fluids for treatment of prerenal ARF due to hypovolemia should be tailored according to the composition of the lost fluid. Severe

hypovolemia due to hemorrhage should be corrected with packed red cells, whereas isotonic saline is usually appropriate replacement for mild to moderate hemorrhage or plasma loss (e.g., burns, pancreatitis). Urinary and gastrointestinal fluids can vary greatly in composition but are usually hypotonic. Hypotonic solutions (e.g., 0.45 % saline) are usually recommended as initial replacement in patients with prerenal ARF due to increased urinary or gastrointestinal fluid losses, although isotonic saline may be more appropriate in severe cases. Subsequent therapy should be based on measurements of the volume and ionic content of excreted or drained fluids. Serum potassium and acid-base status should be monitored carefully, and potassium and bicarbonate supplemented as appropriate. Cardiac failure may require aggressive management with inotropic agents, preload and afterload reducing agents, antiarrhythmic drugs, and mechanical aids such as intraaortic balloon pumps. Invasive hemodynamic monitoring may be required in selected cases to guide therapy for complications in patients in whom clinical assessment of cardiovascular function and intravascular volume is difficult.

Fluid management may be particularly challenging in patients with cirrhosis complicated by ascites. In this setting, it is important to distinguish between full-blown HRS, which carries a grave prognosis, and reversible ARF due to true or "effective" hypovolemia induced by overzealous use of diuretics or sepsis (e.g., spontaneous bacterial peritonitis). The contribution of hypovolemia to ARF can be definitively assessed only by administration of a fluid challenge. Fluids should be administered slowly and titrated to jugular venous pressure and, if necessary, central venous and pulmonary capillary wedge pressure. Patients with a reversible prerenal component typically have an increase in urine output and fall in serum creatinine with fluid challenge, whereas patients with HRS do not. Patients with HRS may suffer increased ascites

formation and pulmonary compromise if not monitored closely during fluid challenge. Large volumes of ascitic fluid can usually be drained by paracentesis without deterioration in renal function if intravenous albumin is administered simultaneously. Indeed, "large-volume paracentesis" may afford an increase in GFR, likely by lowering intraabdominal pressure and improving flow in renal veins. Alternatively, for patients with refractory ascites, transjugular intrahepatic portosystemic shunting is an alternative. Older peritoneal-venous shunts (LaVeen or Denver shunt) have largely fallen out of favor. Transjugular intrahepatic portosystemic shunts may improve renal function through increased central blood volume and suppression of aldosterone and norepinephrine secretion.

Intrinsic ARF. Many different approaches to attenuate injury or hasten recovery have been tested in ischemic and nephrotoxic AKI. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, loop-blocking diuretics, calcium channel blockers, adrenoreceptor blockers, prostaglandin analogues, antioxidants, antibodies against leukocyte adhesion molecules, and insulin-like growth factor type I. Whereas many of these are beneficial in experimental models of ischemic or nephrotoxic ATN, they have either failed to confer consistent benefit or proved ineffective in humans.

ARF due to other intrinsic renal diseases such as acute glomerulonephritis or vasculitis may respond to immunosuppressive agents (glucocorticoids, alkylating agents, and/or plasmapheresis, depending on the primary pathology). Glucocorticoids also may hasten remission in allergic interstitial nephritis, although data are limited to small-case series. Aggressive control of systemic arterial pressure is of paramount importance in limiting renal injury in malignant

hypertensive nephrosclerosis. Hypertension and ARF due to scleroderma may be exquisitely sensitive to treatment with ACE inhibitors.

Postrenal ARF. Management of postrenal ARF requires close collaboration between nephrologist, urologist, and radiologist. Obstruction of the urethra or bladder neck is usually managed initially by transurethral or suprapubic placement of a bladder catheter, which provides temporary relief, while the obstructing lesion is identified and treated definitively. Similarly, ureteric obstruction may be treated initially by percutaneous catheterization of the dilated renal pelvis or ureter. Indeed, obstructing lesions can often be removed percutaneously (e.g., calculus, sloughed papilla) or bypassed by insertion of a ureteric stent (e.g., carcinoma). Most patients experience an appropriate diuresis for several days following relief of obstruction. Approximately 5 % of patients develop a transient salt-wasting syndrome that may require administration of intravenous saline to maintain blood pressure.

Supportive Measures

Following correction of hypovolemia, salt and water intake are tailored to match losses. Hypervolemia can usually be managed by restriction of salt and water intake and diuretics. Indeed, there is, as yet, no proven rationale for administration of diuretics in ARF except to treat this complication. Despite the fact that subpressor doses of dopamine may transiently promote salt and water excretion by increasing renal blood flow and GFR and by inhibiting tubule sodium reabsorption, subpressor (“low-dose”, “renal-dose”) dopamine has proved ineffective in clinical trials, may trigger arrhythmias, and should not be used as a renoprotective agent in this setting. Ultrafiltration or dialysis is used to treat severe

hypervolemia when conservative measures fail. Hyponatremia and hypoosmolality can usually be controlled by restriction of free water intake. Conversely, hypernatremia is treated by administration of water or intravenous hypotonic saline or isotonic dextrose-containing solutions. The management of hyperkalemia is described in.

Metabolic acidosis is not usually treated unless serum bicarbonate concentration falls below 15 mmol/L or arterial pH falls below 7.2. More severe acidosis is corrected by oral or intravenous sodium bicarbonate. Initial rates of replacement are guided by estimates of bicarbonate deficit and adjusted thereafter according to serum levels. Patients should be monitored for complications of sodium bicarbonate administration such as hypervolemia, metabolic alkalosis, hypocalcemia, and hypokalemia. From a practical point of view, most patients who require supplemental sodium bicarbonate administration will need emergency dialysis within days. Hyperphosphatemia is usually controlled by restriction of dietary phosphate and by oral phosphate binders (calcium carbonate, calcium acetate, sevalamer, and aluminum hydroxide) to reduce gastrointestinal absorption of phosphate. Hypocalcemia does not usually require treatment unless severe, as may occur with rhabdomyolysis or pancreatitis or following administration of bicarbonate. Hyperuricemia is typically mild [<890 mol/L (<15 mg/dL)] and does not require intervention.

The objective of *nutritional management* during the maintenance phase of ARF is to provide sufficient calories and protein to minimize catabolism. Nutritional requirements will vary based on the underlying disease process; for example, those with sepsis-associated AKI are likely to be hypercatabolic. The presence of oliguria complicates nutritional management, and if the patient is not on dialysis, minimizing production of nitrogenous waste is a consideration. Often, the institution of dialysis facilitates the provision of

adequate nutritional support. There is no clear benefit of parenteral nutrition compared with enteral nutrition; indeed, those supported with parenteral nutrition are at increased risk of complications, including infection.

Anemia may necessitate blood transfusion if severe. Recombinant human erythropoietin is rarely used in ARF because bone marrow resistance to erythropoietin is common, and more immediate treatment of anemia (if any) is required. Uremic bleeding may respond to administration of desmopressin or estrogens. Often dialysis is instituted to control bleeding that appears to be related to uremia. Gastrointestinal prophylaxis with histamine receptor (H2) antagonists or proton pump inhibitors should be prescribed, especially in the setting of critical illness. Meticulous care of intravenous and bladder catheters, and other invasive devices is mandatory to avoid infections.

Indications and Modalities of Dialysis

During ARF, dialysis is often used to support renal function until renal repair/recovery occur. Absolute indications for dialysis include symptoms or signs of the uremic syndrome and management of refractory hypervolemia, hyperkalemia, or acidosis. Many nephrologists also initiate dialysis empirically for blood urea levels of >100 mg/dL; however, this approach has yet to be validated in controlled clinical trials. Although direct clinical comparisons are limited, hemodialysis appears to be somewhat more effective than peritoneal dialysis for management of ARF. Peritoneal dialysis may be useful when hemodialysis is unavailable or if it is impossible to obtain vascular access. However, peritoneal dialysis is associated with increased protein losses and is contraindicated in those patients who have undergone recent abdominal surgery or those with ongoing infection. Peritoneal dialysis access requires insertion

of a cuffed catheter into the peritoneal cavity.

Vascular access for hemodialysis requires insertion of a temporary double-lumen hemodialysis catheter into the internal jugular or femoral vein. Insertion into the subclavian vein is generally avoided owing to the risk of subclavian stenosis. Hemodialysis may be provided in the form of intermittent hemodialysis (typically performed for 3–4 hours per day, 3–4 times per week), slow low-efficiency dialysis (performed for 6–12 hours per day, 3–6 times per week), or continuous renal replacement therapy (CRRT). CCRTs are particular valuable techniques in patients in whom intermittent therapy fails to control hypervolemia, uremia, or acidosis or in those who do not tolerate intermittent hemodialysis due to hemodynamic instability. In those patients where hemodynamic instability is a primary consideration, slow low-efficiency hemodialysis (SLED), a relatively new hybrid mode of dialysis, is an excellent alternative to CRRT.

Continuous arteriovenous modalities [continuous arteriovenous hemofiltration, hemodialysis, and hemodiafiltration (CAVH, CAVHD, and CAVHDF, respectively)] require both arterial and venous access. The patient's own blood pressure generates an ultrafiltrate of plasma across a porous biocompatible dialysis membrane. With the advent of peristaltic pumps, the arteriovenous modalities have fallen out of favor, in part because of the complications associated with cannulation of a large artery with a large bore catheter. In continuous venovenous hemodialysis (CVVHD), a blood pump generates ultrafiltration pressure across the dialysis membrane. In continuous venovenous hemofiltration (CVVH), the hemodialysis (diffusive clearance) component is eliminated, and an ultrafiltrate of plasma is removed across the dialysis membrane and replaced by a physiologic crystalloid solution (convective clearance). In continuous venovenous hemodiafiltration (CVVHDF), these two methods of clearance

are combined. The bulk of evidence to date suggests that intermittent and continuous dialytic therapies are equally effective for the treatment of ARF. The choice of technique is currently tailored to the specific needs of the patient, the resources of the institution, and the expertise of the physician. Potential disadvantages of continuous techniques include the need for prolonged immobilization, systemic anticoagulation and prolonged exposure of blood to synthetic (albeit biocompatible) dialysis membranes.

The optimal dose of dialysis for ARF remains unclear at present. Recent evidence (from a single center, nonrandomized trial) suggests that more intensive hemodialysis (e.g., daily rather than alternate-day intermittent dialysis) may be clinically superior and confers improved survival in ARF once dialysis is required. This conclusion may not be as intuitive as it first appears since dialysis itself has been postulated to prolong ARF by inducing hypotension and other adverse effects related to the blood-dialyzer contact (e.g., complement activation and inflammation). Similarly, data suggest that increased doses of continuous renal replacement therapy may be of benefit for ARF, although these results need to be confirmed in a larger, multicenter study.

Management of ARF

The following discussion of management in ARF is broadly evidence based. However, it should be recognized that only a few studies in the clinical trial literature relating to management of ARF have prospectively randomized "like subjects" into control and study groups or been sufficiently powered to avoid missing clinically significant effects of the treatments being investigated. In this interpretation of current practices, areas of controversy are highlighted. Specific management strategies for vascular, glomerular, and interstitial processes giving rise to ARF are not discussed.

Principles of Management in Prerenal ARF

Treatment of prerenal ARF is directed towards restoring RBF and tissue oxygenation to normal as early as possible. For most patients restoration of renal perfusion is gratifyingly easy and rapidly effective. It is always necessary to address the underlying cause. Withdrawal of an NSAID or temporary withdrawal and reduction of diuretic dose may help in both the recovery and prevention of further prerenal insult. Avoidance of unnecessary exposure to other nephrotoxic agents, such as radiocontrast dye, while in a prerenal and, therefore, primed state for nephrotoxicity is vitally important.

When volume depletion is the cause of pre-renal azotemia, infusion of blood or saline is indicated, depending on the clinical circumstance. In edematous states complicating heart failure or liver failure, intravascular volume may also be low despite increases in total body salt and water. In general, volume expansion can be guided by careful serial clinical evaluations of volume status. However, in the critically ill patient with hypotension of unclear etiology, more precise definition of cardiac filling pressures and cardiac output may be required. In these cases, right heart catheterization is often employed to guide therapeutic decision making. Although the efficacy and safety of right heart catheterization has been demonstrated in certain subgroups of patients, a large observational study has recently questioned its safety for a significant proportion of critically ill patients in whom it is used. As a result, there is a growing consensus (see comments published in JAMA regarding paper by Connors) that the role of right heart catheterization needs to be studied by randomized clinical trials in those broad groups of patients for whom contro- versy surrounds its risks and benefits. In the interim, many believe the procedure to be a crucial diagnostic tool which in the hands of operators experienced in its use and

interpretation can provide valuable information in the care of seriously ill patients.

Prevention or Reduction of Tubular Cell Injury

Given the high morbidity and mortality as- sociated with ARF, prevention is crucial. Strategies include maintaining an adequate intravascular volume; avoiding nephrotoxic exposure; saline expansion prior to, during, and after radiocontrast exposure in at-risk patients; titrating drug dosages to the level of renal function; understanding the vagaries involved in estimating GFR from serum chemistries in the elderly, the poorly nourished, and those whose blood chemistries are not in steady-state; and monitoring drug levels.

Restoration of RBF with early and active volume replacement may reduce renal tubular cell injury in the initiation phases of ischemic ATN. In nephrotoxic ATN, a forced saline diuresis may reduce the absorptive concentration of nephrotoxins in the tubular cells and renal interstitium, partly abrogating injury. This type of approach must always be tempered to the clinical situation with great care to avoid volume overloading critically ill patients or those with tenuous cardiac status.

Pharmacologic interventions with proven success in the prophylaxis of ARF are few. Allopurinol is beneficial as a pretreatment to chemotherapy in the prophylaxis of acute uric acid nephropathy following tumor lysis. Mannitol administered prior to clamp removal and reperfusion has been shown to be beneficial in improving postoperative graft function in kidney transplantation.

The prophylactic value of mannitol in other clinical settings is unproved. In fact, mannitol has been associated itself with causing ARF. Furosemide is also of doubtful prophylactic value, and its use may even negatively influence outcomes, as

appears to be the case following radiocontrast exposure. The strategies employed to reduce tubular cell injury in early and established ARF are similar to those used for primary prevention. No beneficial role has been demonstrated for either mannitol or furosemide in affecting the course or outcome of established disease.

A controversial pharmacologic intervention in ARF is the use of "renal-dose"/"low-dose" dopamine to prevent the development of, or lessen the severity of, early or estab- lished ATN. To determine the utility of "low-dose" dopamine in preventing ATN, it has been estimated that if the incidence of new onset renal failure in a study were 20 %, then 400 patients would be needed for the study to have 80 % power to detect a 10% risk reduction at the 0.05 level of statistical significance. Based on this observation, no study has ever conclusively addressed the primary preventative value of dopamine in ARF. The current evidence, such as it is, however, provides no substance to the claim that dopamine has a role in the prophylaxis of ARF in high-risk patients.

In those with early or established disease, good evidence for an effect is also lacking. In a small controlled study in ARF, it has been suggested that dopamine and furosemide were superior to furosemide alone. However, this observation is hardly generalizable. A thorough review of papers in this area concluded that low-dose dopamine was apparently ineffective in humans in preventing ARF or improving outcomes in early or established ARF. A posthoc analysis of the Auriculin study group, which attempted to control for confounding factors and bias, also suggested that the use of low-dose dopamine confers no benefit in ARF. As with primary prevention, however, a definitive clinical trial has not been done.

Dopamine is associated with documented significant complications, including tachyarrhythmias and myocardial

ischemia. Experimental data indicate an implied risk also exists for selective mucosal ischemia in the gut, with potential for enhanced bacterial translocation and subsequent systemic sepsis. Use of "low-dose" dopamine has, up until recently, been very prevalent. This usage has been partly driven by the lack of other effective therapies and by a wealth of experimental evidence in animals suggesting that "low-dose" dopamine has beneficial effects on a variety of the factors involved in maintaining oxygen homeostasis in the renal outer medullary nephron segments. Justification of use of "low-dose" dopamine in patients, however, awaits a randomized, prospective, placebocontrolled clinical trial demonstrating both its safety and efficacy. The use of dopamine in pressor doses, with a view to protecting blood pressure and vital organ perfusion, remains clearly necessary and justified in some critically ill patients.

Atrial natriuretic peptide (ANP) is yet another agent of interest in early and established ATN. Through a series of mechanisms on transport processes and vascular smooth muscle tone, it has the potential to enhance GFR while sparing workload and oxygen demand in critically ischemic tubular segments. A recent well-designed prospective, randomized trial has reported on this agent in 504 critically ill patients with ATN.

Calcium channel blockers have been used with some success in ameliorating renal insuf- ficiency in the short term after renal transplantation. Whether this reflects a salutary effect on renal tubular cells of a decrease in cytosolic free calcium concentration, or is mediated by effects on renal perfusion or immune mechanisms is unclear. In transplantation, calcium channel blockers appear to be effective in reducing cyclosporine toxicity via the presumptive inhibition of cyclosporine-dependent vasoconstriction. It has also been suggested that inhibition of contrast-induced vasoconstriction

by calcium channel blockers might be renoprotective. However, calcium channel blockers are potentially hypotensive agents. In general, they are neither routinely used nor believed to have a major role in the prevention or treatment of ATN.

General Supportive Therapy

From a volume standpoint, it is necessary to restrict salt and water intake in euvolemic patients with oliguric ATN to approximately 2 g and 1 L per day, respectively. This greatly limits space for alimentation or intravenous medications. It is particularly suited to situ- ations in which rapid functional recovery and diuresis is anticipated. In the early stages of oliguric ATN, 1–2 high-dose intravenous therapies (80–400 mg) of furosemide may induce diuresis following adequate volume replacement. The goal of this therapy is to assist in volume management of the patient, not to favorably influence the course of the disease. In nonoliguric ARF, more liberal fluid intake replacing urine output and insen- sible losses to maintain a euvolemic state is advised.

The general inability of the kidney in ATN to handle excess free water and elaborate hypotonic urine underlies the propensity in ATN toward development of hyponatremia. Avoiding excess intake of fluids low in effective osmolytes, such as water, dextrose, and hypotonic saline solutions, can prevent this. Hypernatremia is a less common development, which, in the absence of administration of hypertonic saline solutions, almost always implies a combined salt and water deficit that needs to be corrected.

Hyperkalemia often accompanies ARF and may be more exaggerated in settings of tissue breakdown, such as in rhabdomyolysis. ECG changes, e.g. QRS widening, p wave flattening and/or arrhythmias, are signs to provide intravenous calcium as a stabilizer to the myocardium. Insulin and dextrose

infusions, intra- venous bicarbonate, and, in selected patients, nebulized beta-agonists can be used to promote a shift of potassium into the intracellular compartment. Anion exchange resins and/or loop diuretics and/or dialysis serve to remove potassium from the body. Avoidance of drugs, such as ACE inhibitors, potassiumsparing diuretics, potassium supplements and beta- blockers together with dietary potassium restriction may help prevent hyperkalemia. Hypokalemia is less commonly seen in ATN but should be corrected carefully as it is inde- pendently arrhythmogenic, enhances the arrhythmogenicity of other drugs, e.g., digoxin, and may enhance the nephrotoxicity of aminoglycoside antibiotics.

Hyperphosphatemia is a frequent finding managed by dietary restriction and orally ad- ministered phosphate binders. Infrequently, hyperphosphatemia is severe enough to raise the calcium-phosphate product to a point where dialysis is required to prevent metastatic calcification. Magnesiumcontaining antacids are best avoided in ATN to prevent hypermagnesemia. Homeostatic alterations in the humoral control of calcium balance, i.e. low 1-25 dihydroxy-vitamin D3 levels, PTH resistance, sometimes together with tissue uptake of ionized free calcium, as in pancreatitis or evolving rhabdomyolysis, may precipitate symptomatic hypocalcemia requiring the administration of intravenous calcium. Hyperuricemia, while generally present, is rarely of a degree requiring treatment. Levels greater than 15 mg/mL, however, raise the possibility of acute uric acid nephropathy and require treatment with allopurinol.

Finally, the accumulation of fixed acids and nitrogenous waste products from protein catabolism contribute to the development of an anion gap acidosis and other features of uremia. Complex acid-base perturbations may accompany the critically ill patient. Mixed disorders with retention of volatile and fixed acids and/or increased gastrointestinal bicarbonate

losses can complicate respiratory and renal impairment in a surgical or medical patient and be particularly severe. Such disorders require careful monitoring and aggressive management. Ventilation and/or dialysis offer rapidly effective ways to raise pH in a patient with combined respiratory and metabolic acidosis. In the uncomplicated patient with ARF, short-term restriction of dietary protein intake to approximately 0.6 g/kg/day can retard the accumulation of protein catabolites. This is a very undesirable approach in the hypercatabolic patient in whom protein catabolic rates may exceed 200 g of protein/day.

Nutritional Support

Malnutrition is common in ARF. A hypercatabolic state results from: mediators of the systemic inflammatory response syndrome; metabolic and hormonal derangements, such as metabolic acidosis, insulin resistance, and hyperparathyroidism; medications; and aggravating effects of uremic toxins. Compounding this, both inadequate nutritional supplementation and impaired utilization of nutrients can lead to profound proteinenergy malnutrition.

Although nutritional supplementation is proposed to reduce morbidity and mortality, a beneficial effect in ARF has never been conclusively demonstrated. Nonetheless, attempting to supply adequate caloric and protein support to critically ill patients appears intuitively the correct approach. Enteral supplementation is preferable to parenteral treatment whenever possible. Provision of nutritional support can give rise to complications, including infections, volume overload, hyperglycemia, hypertriglyceridemia, hypokalemia and increases in uremic end products of protein metabolism. In oliguric ARF, nutritional support often requires support with complementary renal replacement therapy.

Renal Replacement Therapy

Renal replacement therapy (RRT) replaces nonendocrine kidney function in patients with renal failure and is occasionally used for some forms of poisoning. Techniques include intermittent hemodialysis, continuous hemofiltration and hemodialysis, and peritoneal dialysis. All modalities exchange solute and remove fluid from the blood, using dialysis and filtration across permeable membranes.

RRT does not correct the endocrine abnormalities (decreased erythropoietin and 1,25-dihydroxyvitamin D3 production) of renal failure. During dialysis, serum solute (e.g., sodium, chloride, potassium, bicarbonate, calcium, magnesium, phosphate, urea, creatinine, uric acid) diffuses passively between fluid compartments down a concentration gradient (diffusive transport). During filtration, serum water passes between compartments down a hydrostatic pressure gradient, dragging solute with it (convective transport). The two processes are often used in combination (hemodiafiltration). Hemoperfusion is a rarely used technique that removes toxins by flowing blood over a bed of adsorbent material (usually a resin compound or charcoal).

Dialysis and filtration can be done intermittently or continuously. Continuous therapy is used almost exclusively for acute kidney injury. Continuous therapy is sometimes better tolerated than intermittent therapy in unstable patients because solute and water are removed more slowly. All forms of RRT except peritoneal dialysis require vascular access; continuous techniques require a direct arteriovenous or venovenous circuit.

The choice of technique depends on multiple factors, including the primary need (e.g., solute or water removal or both), underlying indication (e.g., acute or chronic kidney failure, poisoning), vascular access, hemodynamic stability,

availability, local expertise, and patient preference and capability (e.g., for home dialysis).

Table 5 - Indications and Contraindications to Common Renal Replacement Therapies

Renal Replacement Therapy	**Indications**	**Contraindications**
Hemodialysis	Renal insufficiency or failure (acute or chronic) with any of the following that cannot otherwise be controlled: Fluid overload (including refractory heart failure) Hyperkalemia Hypercalcemia Metabolic acidosis Pericarditis Uremic symptoms GFR* <10 mL/min/1.73 m^2 BSA (chronic kidney disease, no diabetes) GFR* <15 mL/min/1.73 m^2 BSA (chronic kidney disease, diabetes) Some poisonings	Uncooperative or hemodynamically unstable patient
Peritoneal dialysis	Same indications as for hemodialysis (except for poisonings) in patients who Have inadequate vascular access or Prefer self-therapy	Absolute: Loss of peritoneal function Adhesions that limit dialysate flow Recent abdominal wounds

Continuation of Table 5

Renal Replacement Therapy	**Indications**	**Contraindications**
		Abdominal fistulas Abdominal wall defects that prevent effective dialysis or increase infection risk (e.g., irreparable inguinal or diaphragmatic hernia, bladder extrophy) Patient's condition not amenable to dialysis Relative: Abdominal wall infection Frequent episodes of diverticulitis Inability to tolerate large volumes of peritoneal dialysate Inflammatory bowel disease Ischemic colitis Morbid obesity Peritoneal leaks Severe undernutrition
Hemoperfusion	Poisoning or toxicity (e.g., due to barbiturates, many antidepressants, ethchlorvynol, meprobamate, paraquat, glutethimide, metals such as lithium and barium, or toxic doses of aminoglycosides or cardiovascular drugs)	Uncooperative or hemodynamically unstable patient

CHRONIC RENAL FAILURE (CRF)

Chronic renal failure is a progressive loss of kidney functions due to progressive damage of kidney tissue by a disease involving the two kidneys.

In chronic renal failure, there is a persistent and irreversible reduction in the overall renal function. Not only the excretory functions are disturbed but also the endocrine and the haemopoietic functions as well as the regulation of acid-base balance become abnormal. These derangements in the internal environment (internal milieu) of the body will result in the uremic syndrome.

In this domain there are confusions caused by use of different terms which could be solved by putting them in acceptable definitions. These terms and their definitions are as the following:

Azotaemia: This means that the concentrations of the blood urea and the blood urea nitrogen (BUN) are raised. It is not necessary that the patient has uremic symptoms. Kidney function could even be normal and accumulation of urea is due to dietary causes, pre renal factors or even from laboratory interference.

Uraemia: is the syndrome resulting from severe renal failure.

Renal impairment: this means that there is a reduction in GFR which is still not severe enough to produce significant uremic symptoms.

End stage renal failure (ESRF) is considered when chronic renal failure is so severe that the patient cannot live without renal replacement therapy (dialysis or transplantation). This is sometimes called terminal renal failure or terminal uraemia.

Disease involving one kidney (even if very severe and damaging this kidney) will not result in renal impairment or

failure as the other kidney is capable to maintain the internal milieu or environment within normal. In this setting we may say compromised or non-functioning right or left kidney (according to the kidney damaged right or left). Sometimes we say solitary functioning right or left kidney (according to the side of the healthy kidney).

INCIDENCE OF CHRONIC RENAL FAILURE

This varies from one country to the other. For example, in western Europe and Australia the incidence is about 50 new cases per million population per year. In USA, the incidence is 160 new patients / million per year, while in Egypt and some developing countries it is believed to be about 200 new patients/million population per year. This variability could be attributed to different socio-economic and environmental factors.

AETIOLOGY OF CHRONIC RENAL FAILURE

The common causes of CFR are diabetic nephropathy, chronic pyelonephritis, obstructive uropathy, reflux nephropathy, chronic glomerulonephritis and polycystic kidney disease. The complete list of causes includes the following:

1 Primary GlomerularDdiseases:

These are idiopathic crescentic glomerulonephritis, primary focal segmental glomerulosclerosis and primary mesangiocapillary glomerulonephritis.

2 Tubulo-Interstitial Diseases:

These include the following:

- Chronic heavy metal poisoning such as lead, cadmium and mercury may result in chronic tubulo-interstitial nephritis and renal failure.
- Chronic hypercalcaemia as with vitamin D intoxication and primary hyperparathyroidism.
- Chronic potassium depletion resulting from prolonged use of diuretics without potassium supplementation as in patients with ascites or chronic heart failure.

3 Renal Vascular Diseases:

These may be in the main renal vessels (artery or vein) or in the intrarenal vessels.

Main renal artery diseases causing renal failure:

Renal failure may occur if there is bilateral advanced renal artery stenosis or a unilateral renal artery stenosis in a solitary kidney.

Renal artery stenosis usually occurs due to advanced atherosclerosis which is more common in elderly males or due to fibromuscular dysplasia which is more common in middle aged females.

Both atherosclerosis and fibromuscular dysplasia are manifested, first, by renovascular hypertension. Later, they may end by renal failure due to progressive renal ischaemia.

Renal vein diseases causing renal failure:

Bilateral renal vein thrombosis, which is more common in patients with nephrotic syndrome. In bilateral thrombosis or thrombosis of the sole kidney, it can lead to renal failure.

Small renal vessel diseases causing chronic renal failure:

Example of these diseases are nephrosclerosis secondary to long standing hypertension (very common), polyarteritis nodosa (less common), or malignant hypertension.

4 Chronic Urinary Tract Infection:

Chronic pyelonephritis is considered the most common cause of chronic renal failure in our locality. It may be caused by a specific organism as in tuberculous pyelonephritis or by nonspecific organisms such as E.coli.

5 Chronic Urinary Tract Obstruction:

This may be upper or lower urinary tract obstruction. It results in hydronephrosis which if left untreated may result in CFR.

Causes of upper urinary tract obstruction include bilateral ureteric or renal stones, bilateral neoplasms and bilateral ureteric stricture.

Causes of lower urinary tract obstruction include bladder tumour, senile prostatic enlargement, huge bladder stones and stricture urethra

Association of infection and obstruction is the most common cause of renal failure as obstruction may invite infection and infection may lead to obstruction.

6 Collagen Diseases:

Collagen diseases such as S.L.E. and polyarteritis nodosa, rheumatoid arthritis, and systemic sclerosis may cause chronic renal failure. These diseases cause renal failure either through a direct renal involvement by the disease itself or as a complication of the disease (in rheumatoid artheritis renal failure may be caused by secondary amyloidosis or by drug used as NSAIDs and cytotoxic drugs).

7 Metabolic Diseases:

Renal amyloidosis; which is usually a complication of Familial Mediterranean Fever (FMF) or chronic suppuration (e.g., osteomyelitis) may end by chronic renal failure.

Gout may cause chronic renal failure either directly (gouty nephropathy) or secondary to abuse of NSAIDs. More commonly it develops by the two mechanisms.

Diabetic nephropathy is one of the common causes of CFR.

Analgesic nephropathy occurs with most of non-steroidal antiinflammatory drugs (NSAIDs) such as aspirin. Analgesic nephropathy is a cumulative effect needing a long term drug administration. Nearly an amount of 2-3 kgm of aspirin is needed for chronic renal failure to occur. This condition is frequently seen in patients with chronic pain as those with osteoarthritis and rheumatoid arthritis.

PATHOPHYSIOLOGY OF CHRONIC RENAL FAILURE

1 Disturbance of Water Excretion:

Total body water is a major determinant of its solute concentrations. Keeping the total body water within the normal range is mandatory for keeping the body internal milieu. The kidney is the major determinant for adjusting total body water. This is achieved through it's capacity to dilute and to concentrate urine. With chronic renal failure, this capacity is deranged as the following:

A Loss of the renal ability to concentrate urine: this occurs early in renal failure leading to nocturia and polyuria. This is due to the fact that with kidney damage the number of functioning nephrons is decreasing while the amount of osmotically active molecules produced by the body is stable (about 600 mosmol/day). This will create an osmotic load on the functioning nephrons with subsequent polyuria. If water intake is decreased or if there is fluid loss (e.g., vomiting or diarrhea), the urine volume will not decrease in parallel, but rather a little decrease will occur (due to decrease renal blood

flow). As the kidney is unable to concentrate urine to excrete more toxins, retention of wastes will occur. Furthermore, dehydration will result in renal ischaemia which will aggravate the renal damage. When urine osmolarity is as plasma (300 mosmol/L), at least 2000 c.c. of urine is needed for excretion of the daily produced wastes which is the situation in uremic patients, while in normal kidney only 500 c.c. of maximally concentrated urine (1200 mosmol/L) are sufficient.

B Loss of the renal ability to dilute urine: This occurs late in renal failure. If the uremic patient receives excess fluid he may pass into fluid overload, even pulmonary oedema. In normal persons, urine osmolarity can dicrese to 50 mosmol/L (specific gravity 1.001), i.e. urine is hypotonic with respect to plasma, whereas in progressive uraemia, the dilution will decrease only to 300 mosmol (S.G. 1.010), i.e. equal to plasma. In addition, the diseased kidney will dilute urine very slowly in comparison to the intact one.

2 Disturbance of Sodium Excretion:

As renal failure progresses, the ability of the nephron to adjust sodium balance decreases.

The following disorders may occur:

A Hyponatraemia, usually dilutional hyponatraemia that is due to retention of excess water taken along with salt loss such as with sweating, vomiting, and diarrhoea.

B Salt and water retention which can cause hypertension.

C Salt-losing nephropathy which occurs in diseases such as analgesic nephropathy, cystic kidney diseases, and tubulointerstitial nephritis. This will manifest with hypovolaemia, dehydration and hypotension, which if not treated (by excess salt intake) may lead to acute on chronic renal failure.

3 Disturbed Potassium Excretion:

The kidney has a high capacity to excrete potassium. Accordingly serious hyperkalaemia rarely occurs unless GFR is less than 10ml/min. Other reasons for hyperkalaemia should be looked for if GFR is more than 10 ml/min, these are:

- Excess potassium load
- Hyporeninaemic hypoaldosteronism
- Severe acidosis with volume contraction
- Drugs as ACEI, B-blockers, and aldosterone antagonists.

4 Disturbance of Acid-Base Balance:

Chronic renal failure may result in metabolic acidosis which will manifest in advanced stages by Kussmaul's breathing (air hunger). In cases with tubulo interstitial diseases, acidosis may manifest earlier (discrepant with serum creatinine). This condition will be aggravated by increased acid load and sodium depletion.

With chronic acidosis, bone will be used as a buffer with consequent skeletal calcium loss and bone disease.

Metabolic acidosis in uremic patient is due to the following:

A Decrease in titratable acid (phosphates, sulfates, etc.) excretion due to decreased GFR;

B Decrease in ammonia production by the proximal convoluted tubules; and

C Bicarbonate wastage.

5 Disturbance of Calcium-Phosphate Metabolism:

This disorder could be summarized as the following:

A Retention hyperphosphataemia: As the kidney is the main route of phosphate elimination, decrease of GFR below 30 ml/min will be accompanied by hyperphosphataemia. At first, this may occur transiently, but later it may be persistent. In earlier phases of uraemia, hyperphosphataemia may occur post-prandially, especially with meals heavy in protein and dairy products.

B Hypocalcaemia: due to the dynamic equilibrium between serum calcium and phosphate, hypocalcaemia will occur with any increase in serum phosphate. Other causes of hypocalcaemia in uremic patient are defective activation of vitamin D in PCT and decreased dietetic intake.

C Hyperparathyroidism: will occur in response to hypocalcaemia. Secondary hyperparathyroidism will result in bone demineralization through osteoclast activation. This occurs in attempts to correct hypocalcaemia. With correction of hypocalcemia, parathyroid activity is arrested, yet as phosphate is high, deposition of phosphate and calcium in soft tissues will occur to keep the dynamic equilibrium (serum Ca X serum Po4=50). Again, calcium level gets low and parathyroid gland becomes active with consequent bone demineralization. So far the uraemia persists, this viscious cricle will keep active. Long term stimulation of parathyroid gland will result in development of adenoma which is autonomus i.e despite calcium is getting high parathyroid gland will keep secreting parathromone (tertiary hyperparathyroidism). This will lead to more aggressive bone disease and soft tissue calcification. In addition, it will lead to bone fibrosis and aggravation of anemia.

D A bone disease, sometimes called renal osteodystrophy; it is due to multiple factors, including negative calcium and protein balance, lack of active vit. D, hyperparathyroidism, and aluminium intoxication. Aluminum intoxication is due to long term use of aluminum containing

antacids as phosphate binder and the use of aluminium contaminated water in preperation of dialysate for patients under hemodiamysis treatment.

E Soft tissue calcification: is due to hyperphosphataemia, secondary hyperparathyroidism, mobilization of bone calcium to blood with the consequent increase of the constant value (serum calcium X serum phosphate). Deposition of calcium occurs in all soft tissues including skin, conjunctiva, vessels wall and even the heart.

6 Retention of Uremic Toxins:

These retained toxins are responsible for most of the uremic symptoms, including lethargy, malaise, nausea, vomiting, pericarditis, pleurisy, uremic colitis, platelet dysfunctions, etc.

Removal of these toxins by dialysis is accompanied by an improvement in urate syndrome.

The nature of uremic toxins is yet uncertain. However, they may be:

A Urea, creatinine, uric acid, guanidines, phenols, nucleic acid breakdown products, etc.

B Medium molecules, which are substances with a molecular weight between 300 and 2,000 dalton.

7 Failure of the Renal Hormonal Functions, Including:

Erythropoietin, activation of vitamin D and disturbed Renin excretion

CLINICAL FEATURES OF CHRONIC RENAL FAILURE

1 Gastrointestinal Manifestations:

Mouth: The high concentration of urea in saliva causes unpleasant taste (taste of ammonia) and uremic odour of the mouth (ammoniacal smell).

The tongue appears dry, dirty, brown, or white coated and may be ulcerated. Later, stomatitis, ulceration of the mouth and pharynx may occur. The mouth is always dry due to dehydration and mouth breathing. Dental caries is also common.

Stomach: Gastritis and sometimes gastric erosions may occur. This occurs due to the high concentration of urea in saliva and gastric juice, causing chronic irritation of the gastric mucosa. The patient may suffer from anorexia, nausea, and vomiting. Upper G.I.T. bleeding (haematemesis) and melena may even occur.

Hiccough occurs in terminal stages of uraemia and is aggravated by food. The cause of hiccough in uremic patient is most probably due to irritation of the phrenic nerve or may be due to a central effect induced by uremic toxins.

Intestine: Usually, there is constipation due to dehydration, but diarrhea or even bloody dysentery (uremic dysentery) may occur in terminal uraemia. This is due to urea deposition in the mucosa of the colon which leads to mucosal ulceration which is liable to superadded infection which may cause diarrhea.

In severe cases of mucosal ulceration, there may be bleeding per rectum.

2 Neurological Manifestations:

These include the following:

A Cerebral: Headache, lassitude, drowsiness, insomnia, sometimes inverted sleep rhythm, and vertigo are common manifestations of uraemia. These manifestations are caused by the retained uremic toxins. Uremic coma occurs in advanced cases.

B Neuromuscular: Flabbing tremors (asterixis) and proximal myopathy with paradoxically brisk tendon reflexes. Peripheral neuropathy is usually mixed (motor and sensory) and mainly affecting legs. Patients present mainly with paraesthesia. Muscle twitches and convulsions are mainly due to hypokalaemia and hypocalcaemia. Muscle weakness is due to hyperkalaemia, hyponatraemia and hypovitaminosis D.

3 Hematologic and Cardiovascular Manifestations:

Anemia: It is a common feature of uraemia and usually normocytic normochromic. It is partly responsible for many of the debilitating symptoms of uraemia such as lethargy, tiredness and exertional dyspnea. The main causes of anemia in uremic patients are the following:

- Bone marrow depression due to uremic toxins and erythropoietin deficiency.
- Short life span of R.B.Cs due to the uremic toxins.
- Nutritional deficiency due to dietatic restrictions and dyspepsia (protein, vit. B12, and folic acid).
- Iatrogenic causes as frequent blood sampling in hospitalized patients and the blood loss in the dialyzer at the end of each hemodialysis session.
- Bleeding tendency as GIT bleeding and metrorrhagia.
- Aluminium toxicity.
- Bone marrow fibrosis due to hyperparathyroidism.
- Hypersplenism especially in multiple transfused patients.

Sometimes anemia is microcytic-hypochromic due to iron deficiency.

White cell count and platelet count are normal, but with reduced function.

A Bleeding tendency:

May result from

- Qualitative platelet defects:

Platelet aggregation is reduced and ADP release is inhibited, leading to increased capillary fragility and prolongation of bleeding time.

- Increased fibrinolytic activity of the blood since fibrinolysin is normally excreted by the kidney.
- Anemia:

The tendency to bleed is corrected by dialysis, correction of anemia, or administration of DDAVP or estrogen.

B Hypertension: Hypertension in uremic patients is either due to high renin secretion or salt and water retention. It occurs in about 80 % of cases. In uremics, hypertension is characterised by resistance to drug treatment and by tendency to develop malignant hypertension more than in other forms of hypertension. Hypertension aggravates the renal disease which further increases the blood pressure and a vicious circle is produced.

C Uremic pericarditis:

This occurs due to deposition of urea on the smooth inner surface of the pericardial sac changing it into rough surface. Continuous friction between the visceral and parietal pericardium during cardiac systole and diastole results in dry pericarditis which manifests by pericardial pain and pericardial rub on auscultation. Later, hemopericardium develops which progresses to cause cardiac compression (tamponade). This manifests clinically by a triad of:

1 Progressive systemic venous congestion with congested neck veins, congested liver, and anasarca.

2 Progressive hypotension due to reduction of stroke volume as venous return is progressively decreasing.

3 Progressive increase in cardiac size on clinical examination and by plain X-ray. Echocardiography shows that the enlargement is mainly due to fluid collection in the pericardium. It also shows the defective cardiac filling and reduced stroke volume.

Cardiac tamponade, if not treated urgently, will be fatal. Treatment is by pericardiocentesis. If recurrent, treatment is by making pericardial window (between pericardial sac and pleural sac) or by partial pericardiectomy.

Pericarditis is one of the signs of terminal uraemia which indicates urgent dialysis.

D Heart failure:

This is usually a left sided heart failure which is due to:

- Hypertension.
- Anemia.
- Fluid overload.
- Uremic cardiomyopathy.

4 Cutaneous Manifestations:

- Muddy face (sallow skin), due to retention of some toxins (urochromogens).
- Puffy face due to salt and water retention.
- Pallor due to anemia.
- Dry skin with urea frost (white spots due to deposition of urea present in high concentration in the sweat). Also the skin is fragile, thin and bruises easily.
- Pruritis results from skin dryness or from irritation of the cutaneous sensory nerves by calcium deposits or by parathormone.

- Purpura and skin infection.
- Nails may be white with tips discoloured brown.

5 Respiratory Manifestations:

These include the following:

- Kaussmaul's (acidotic or hissing) breathing.
- Exertional dyspnea, paroxysmal nocturnal dyspnea with heart failure.
- Increased incidence of pulmonary infection.
- Rarely, dry uremic pleurisy.

6 Ocular Manifestations:

These include the following:

- Retinopathy.
- Uremic amaurosis (rare), which is sudden transient loss of vision.
- Red eye due to conjunctival congestion and calcium deposition.
- Calcium may be deposited as plaques in the conjunctiva.

7 Musculo-Skeletal and Soft Tissue Manifestations:

These include the following:

A *Muscular*: fatigue and wasting (myopathy), mostly proximal in lower limbs (Waddling gait). It is due to retained uremic toxins, electrolyte disturbances, vitamin D deficiency, hyperparathyroidism, and nutritional deficiency.

B *Skeletal*: bone aches, fractures, and deformity in childhood cases.

Gout (uric acid deposition) and pseudogout (calcium deposition) cause joint pains.

C *Soft tissue calcification* which manifests according to the tissue involved, e.g., pruritus when skin and sensory nerves are involved, red eye when conjunctiva is affected, arthritis when calcium deposition involves periarticular tissues, and finger tips gangrene when small arterioles are involved (Calcifelaxis).

8 Gonadal Disturbances:

The following gonadal disorders are commonly seen in uremic patients:

- In males: decreased libido, impotence, gynecomastia, reduced spermatogenesis.
- In females: decreased libido, infertility and menstrual dysfunctions.

9 Endocrinal Disturbances:

The following endocrine disorders are common in uremic patients:

- Hyperparathyroidism.
- Lack in activation of vit. D.
- Increased renin activity.
- Lack of erythropoietin.
- Decreased testosterone level resulting in a decreased libido, potency and spermatogenesis.
- Increased prolactin and L.H., causing menstrual disorders, gynecomastia, and infertility.
- Insulin: there are two opposing effects of uraemia on insulin. The first effect is tissue resistance to insulin due to the uremic milieu. The second is decreased renal tubular degradation of insulin with a consequent increase in the insulin half life. The upper hand is usually for the second effect with

consequent fall in insulin requirement (insulin daily dose) in diabetic patients when they become uremic.

10 Features of the Underlying Disease:

They may be present as a manifestation of DM, SLE or renal stone disease.

RENAL PATHOLOGY

1 Gross Appearance:

Usually the kidney is small in size with granular surface and adherent capsule. Sometimes the kidney is normal in size as in diabetic nephropathy and in amyloid nephropathy. In cases secondary to PCKD and hydronephrosis, the kidney size may be larger than normal.

2 Microscopically:

Light microscopy shows diffuse interstitial fibrosis, tubular atrophy and hyalinosis of most of the. The remaining viable glomeruli and tubules are dilated. Sometimes microscopic examination may show the etiologic cause as renal amyloidosis.

INVESTIGATIONS OF A CASE WITH CHRONIC RENAL FAILURE:

1 Urine Examination may show the following**:**

• Polyuria especially nocturia and anuria in terminal cases.

• Urine specific gravity is low and fixed to 1010 (osmolarity 300 mosm/l).
• Urine aspect is pale and watery.
• Albuminuria and granular casts.

2 Blood Changes:

There is an increase in blood urea, creatinine and uric acid levels, metabolic acidosis, normochromic normocytic anemia, hyperkalaemia, and hyperphosphataemia. Serum calcium may be normal or low in early phases, but it becomes high in stage of tertiary hyperparathyroidism.

3 Kidney Function Tests:

Marked impairment of the renal functions (increased serum creatinine and decreased cr. clearance). Plasma creatinine is elevated once GFR is decreased to less than 60 ml/min.

4 Fundus Examination:

It may show uremic retinopathy.

5 Investigations to Know the Cause of Renal Failure:

Such as plain X-ray for urinary tract (stone), ultrasonography (obstruction), blood sugar (diabetes), and anti DNA (SLE). Renal biopsy is indicated in cases with average kidney size and unknown etiology of uraemia.

MANAGEMENT OF CHRONIC RENAL FAILURE

The following steps should be adopted for a proper management of patients with chronic renal failure:

Step 1: CONFIRMATION OF CHRONICITY OF THE KIDNEY DISEASE

This could be achieved through the following:

A History: A long history of renal disease suggests chronicity while absent previous history suggests acute renal failure.

B Kidney size as detected by ultrasonography: A small atrophic kidney favours the diagnosis of chronic renal failure, while a normal sized kidney is more in favour of acute renal failure.

There are some conditions of chronic renal failure in which kidney size is within normal, these are:

- Diabetic nephropathy.
- Renal amyloidosis.
- Infiltration (leukaemia, lymphoma, sarcoidosis).
- PCKD.
- Obstructive uropathy.
- Bilateral staghorn stone.

C Magnitude of the increase in serum creatinine in relation to the presenting symptoms: High serum creatinine with minimal symptoms is in favour of chronic renal disease, while relatively low serum creatinine with severe symptoms is in favour of acute renal disease.

D Hyperphosphataemia and osteodystrophy are present more with chronic cases.

E Anemia is more with chronic cases.

F Renal biopsy: extensive renal interstitial fibrosis and tubular atrophy in renal biopsy are features of chronic cases.

Step 2: SEARCHING FOR REVERSIBLE FACTORS

These factors are classified as the following:

A Pre-renal factors such as:

- Bilateral renal artery stenosis.
- Severe cardiac failure.
- Malignant hypertension.
- Hypotension.
- Dehydration and hypovolaemia.

B Renal causes factors such as:

- Active glomerular disease.
- Active tubulo-interstitial disease.
- Pyelonephritis.

C Postrenal factors: Causing obstruction of urine flow from both kidneys such as:

- Stone.
- Stricture ureters.
- Enlarged prostate.
- Bladder neck obstruction.

Step 3: CONSERVATIVE TREATMENT OF CHRONIC RENAL FAILURE:

A Dietary control:

• *Protein* is usually restricted to 0.6-1 gm/kg/day (an amount which satisfies the physiologic requirements). If uremic symptoms are marked, a further restriction of protein to 0.3 g/k/d may be adopted with addition of supplemental mixture of ketoacids, hydroxy acids and amino acids (10-21 g/d).

Protein restriction will not only decrease the uremic symptoms but also may help in slowing the progression of kidney scarring.

• *Fluid restriction* equivalent to the patient's daily fluid loss. This equals: the sensible water loss (e.g., urine, vomitus, and diarrhea) plus the insensible water loss (respiratory and sweat) which is about 600 ml/d in an adult of 70 kg. Extra 200 ml fluid should be added in febrile patient for every one degree centigrade increase in the body temperature.

• *Electrolytes:* Sodium restriction with hypertension or oedema, and potassium restriction with severe oliguria and with hyperkalaemia.

• *Calories:* The patient should receive about 35 K calories/kg/day, with carbohydrates making up 60 % of non-protein calories and fats 40 %. The ratio of polyunsaturated to saturated fats should be 1:1. The total amount of fiber should be 20-25 gm/day.

B Treatment of Bone disease:

• *Phosphate Binders* such as aluminium hydroxide, magnesium oxide and calcium carbonate or acetate which combine with phosphorus in the gut and are excreted with the stool. Calcium containing compounds are better than aluminium and magnesium salts which could be dangerous on long term use. Calcium carbonate or acetate may be given orally t.d.s. with meals in a dose of 500-1000 mg orally.

• *Active vitamin D* "1-OH vitamin D" which is given orally in a daily dose of 0.25-1.0 μg. Recently,

I.V. 1-OH vitamin D (one-alpha) is recommended for better suppression of the hyperparathyroidism.

This is given in a dose of 0.5-2.0 μg twice or thrice weekly.

• *Acidosis* is corrected by oral Na bicarbonate supplementation.

• *Parathyroidectomy* may be done for cases with tertiary hyperpara - thyroidism. Three glands and part of the fourth are removed and the remaining is implanted subcutaneously.

C Anemia:

It is responsible for major part of uremic symptoms. The first line of treatment is by giving proper nutrition, iron, folic acid, and vitamins especially B12. Failure to respond may indicate repeated blood transfusion or treatment with recombinant human Erythropoietin. Blood transfusion carries the advantage of being cheap, but it has the disadvantage of transmitting diseases (especially HIV, HBV, and HCV) beside other risks of blood transfusion. Erythropoietin (EPO) is given S.C. 4000 u three times weekly; it carries the advantage of being safe and effective, but it is very expensive. The dose of EPO has to be readjusted to maintain haemoglobin value of 9-11 gm/dl. If the patient can't afford for EPO, blood transfusion is preferably given only for symptomatic anemia.

D Symptomatic Treatment of:

• *Hypertension* is controlled by hypotensive drugs. In cases of volume dependent hypertension the main line of treatment is salt and water restriction and diuretics. In cases of renin dependent hypertension, anti-renin such as β-Blockers or ACE inhibitors are used.

• *Itching* is treated by skin soothing creams, anti-histaminics, treatment of hyperphosphataemia, hyper and hypocalcaemia. For severe, intractable cases,

parathyroidectomy may be of help. Sometimes pruritus could be controlled by giving xylocain 70 mg in 100 c.c. saline via I.V. infusion over 20 min. at the end of each dialysis session.

- *G.I.T. manifestations* as vomiting could be controlled by antacids and H2-receptors blockers.

Failure of conservative treatment to provide the patient with a reasonable quality of life is an indication for renal replacement therapy, i.e. dialysis or renal transplantation.

Step 4: RENAL REPLACEMENT THERAPY (RRT):

This includes dialysis (hemodialysis and peritoneal dialysis) and renal transplantation. Early induction of RRT and good nutritional support provide better response to the treatment (less patient morbidity and mortality).

Indications for RRT:

- Failure of conservative treatment with progressive deterioration in patient's general condition and blood chemistry.
- Persistent nausea and vomiting.
- Circulatory overload which is unresponsive to loop diuretics (e.g., frusemide).
- Severe motor neuropathy.
- Uremic encephalopathy.
- Pericarditis.
- Osteodystrophies.
- Bleeding diathesis.
- Hypertension unresponsive to treatment.
- Hyperkalaemia (serum K+ level >7 mEq./litre).
- High creatinine levels and decreased creatinine clearance (Cr. clearance <10ml/min).

Contraindications for Dialysis Treatment:

Absolute:

- Patient's decision (i.e. refusing dialysis).
- Severe extrarenal illness, e.g., severe cardiac disease, end stage liver disease, severe cerebrovascular disease, and advanced malignancy.

Relative:

- Severe disability or handicapping.
- Paraplegia or hemiplegia.

DIALYSIS THERAPY

Definition: Dialysis is a process in which the solute composition of blood is altered by exposing it to a physiological solution (dialysate) across a semipermeable membrane (dialysis membrane). Solutes will move from one compartment to another through the dialysis membrane.

Principles of Dialysis: Solutes that can pass from blood through the pores of the dialysis membrane are transported by two different mechanisms: (1) diffusion and (2) ultrafiltration.

1 Diffusion:

It is the passage of solutes through the semipermeable membrane independent of water movement.

Factors affecting solute diffusion include:

A Concentration Gradient:

The net rate of transfer of a given solute from blood to dialysate is the greatest when the concentration gradient for that particular solute is the highest.

B Molecular Weight and Size:

The larger the M.Wt. of a solute, the slower its rate of transport will be across the semipermeable membrane.

C Membrane Resistance:

Membrane resistance owing to the membrane itself:

The resistance of a membrane to solute transport will be high if the membrane is thick; if the number of pores is small and if the pores are narrow.

Membrane resistance due to "unstirred" fluid layers:

Unstirred layers of fluid inhibit diffusion because they act to decrease the effective concentration gradient at the membrane surface.

2 Ultrafiltration:

The second mechanism of solute transport across semipermeable membrane is ultrafiltration (i.e. convective transport).

Water molecules are extremely small and can pass through all semipermeable membranes. Ultrafiltration occurs when water deriven by either a hydrostatic or osmotic force is pushed through the membrane. Those solutes that can pass easily through the membrane pores are swept along with the water (a process called solvent drag).

Types of Ultrafiltration:

- *Osmotic ultrafiltration:*

This depends on the osmotic pressure of the dialysate. The higher the osmotic pressure, the more the ultrafiltration.

- *Hydrostatic ultrafiltration:*

This depends on the transmembrane pressure; i.e, the higher the transmembrane pressure the more the ultrafiltration. The semipermeable membrane is not permeable to cells or plasma proteins.

Types of Dialysis:

There are two forms of dialysis therapy: (1) hemodialysis, and (2) peritoneal dialysis.

HEMODIALYSIS

Definition: It is the movement of solutes and water from the patient's blood across a semipermeable membrane which is the dialyzer.

This is carried out via vascular access where the blood is pumped by a hemodialysis machine into the dialyzer then the blood returns back filtered to the circulation of patients.

Complications:

Common Complications:

A Hypotension: This is the commonest complication and may be due to:

1) Causes related to excessive decrease in blood volume:

- Fluctuation in the ultrafiltration rate.
- High ultrafiltration rate.
- Target dry body weight set is too low.
- Dialysis solution sodium level is too low.

2) Causes related to lack of vasoconstriction:

- Acetate-containing dialysis solution.
- Dialysis solution is too warm.
- Food ingestion (splanchnic vasodilatation).
- Tissue ischaemia.
- Autonomic neuropathy (e.g., diabetic patients).
- Antihypertensive medications given at the day of dialysis.

3) Causes related to cardiac factors:

- Diastolic dysfunction may be due to
  - Left ventricular hypertrophy.
  - Ischaemic heart disease.
  - Other conditions.
- Failure to increase cardiac rate which may be due to:
  - Intake of beta blockers.
  - Uremic autonomic neuropathy
  - Aging.
- Inability to increase cardiac output for other reasons such as poor myocardial contractility because of age, hypertension or atherosclerosis.

4) Uncommon causes:

- Pericardial tamponade.
- Myocardial infarction.
- Occult haemorrhage.
- Septicaemia.
- Arrhythmia.
- Dialyzer reaction.
- Haemolysis.
- Air embolism.

B Muscle Cramps: The pathogenesis during dialysis is unknown, but the three most important predisposing factors are:

- Hypotension.
- Patient below dry body weight.
- Use of low sodium dialysis solution.

C Nausea and Vomiting: The aetiology is multifactorial, however, most episodes in stable patients are probably related to hypotension. They may be also an early manifestation of the so called disequilibrium syndrome.

D Headache: It may be related to the use of acetate-containing dialysis solution, disequilibrium syndrome. Also it may occur in heavy coffee drinkers as it may be a manifestation of caffeine withdrawal.

E Chest pain and back pain: It may be due to complement activation; thus, there is no management or prevention strategy other than switching to synthetic or substituted cellulose dialysis membrane.

F Itching: It is a common complaint in dialysis patients which may be due to:

- Allergy to
  - Ethylene Oxide (ETO), used for sterilization of the dialysis membrane.
  - Heparin.
  - Plasticizers.
- Elevated calcium-phosphate product.
- Uremic toxins.
- Dry skin.

It can be managed by topical emollients, antihistaminics, phosphate binders and the switch from ETO to gamma ray sterilized dialyzers.

G Fever and Chills: They may be due to a pyrogenic reaction or true sepsis transmitted to the patient during the dialysis session.

Less Common Complications:

Although they are less common, they are serious complications. They include:

A Disequilibrium Syndrome:

Disequilibrium syndrome is a set of systemic and neurologic symptoms which are often associated with characteristic EEG findings that can occur either during or soon after dialysis. Early manifestations include headache, nausea, vomiting, convulsions, and may be coma. In severe cases, death can occur if not treated properly. The etiology is controversial but many believe that it is due to brain odema due to aggressive and rapid dialysis.

Prevention is better, this could be achieved by making the few initial dialysis sessions short and smooth (gradually increasing dialysis hours and blood flow rate).

Treatment of an established case is by stopping dialysis and giving symptomatic treatment, including brain dehydrating drugs as dexamethazon.

B Dialyzer reactions:

Type A (Anaphylactic type): The manifestations of this type may be mild in the form of itching, cough, urticaria, sneezing, coryza or watery eyes; or may be severe in the form of dyspnea, chest tightness, cardiac arrest or even death.

Etiology:

- ETO sterilization.
- ACE inhibitors are caused at the same time with AN 69 type of dialyzer due to liberation of bradykinin.
- Contaminated dialysate: this can be managed by more frequent cleaning and sterilization of dialysis machines between sessions, thus reducing the dialysis solution bacterial counts.

Treatment:

- Stop dialysis immediately.
- Antihistaminics.

- Steroids.

Type B (Non specific type): The patients may complain of back pain or chest pain.

Etiology: Complement activation.

Treatment: No specific treatment.

Arrhythmia: Arrhythmias during dialysis are especially common in patients receiving digitalis.

Cardiac Tamponade: Unexpected or recurrent hypotension during dialysis may be a sign of pericardial effusion or impending tamponade.

Intracranial Bleeding: Underlying vascular disease and hypertension combined with heparin administration can sometimes result in intracarnial bleeding.

Seizures: This occur more often in children

Haemolysis: Acute haemolysis during dialysis may be a medical emergency.

Air Embolism: It is a potential catastrophe that can lead to death if not quickly detected and treated.

PERITONEAL DIALYSIS

Definition: It is the movement of solutes and water from patient's blood across a semipermeable membrane (which is the peritoneal membrane) to the dialysis solution (dialysate).

This is carried out via peritoneal catheter which is inserted into the peritoneal cavity by infusion of the dialysate which is left to dwell then; drain out via the catheter (Fig. 7.6).

Types:

1 CAPD (Continuous Ambulatory Peritoneal Dialysis):

In which the dialysate is always present in the peritoneal cavity and is exchanged every 4-6 hours/day. This is the commonly used form of peritoneal dialysis worldwide.

2 CCPD (Continuous Cyclic Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cycler (P.D. machine) 3-4 times and the last exchange fluid is left in the abdomen during the daytime.

3 NIPD (Nocturnal Intermittent Peritoneal Dialysis):

In which the dialysate is exchanged at bed time via a cycler 5-8 times/day and the abdomen is left dry the rest of the day.

This is the new trend nowadays, but it is limited because of the high cost of the cycler.

4 TPD (Tidal Peritoneal Dialysis):

This is still an experimental form of NIPD which was designed to optimize solute clearance by leaving large volume of dialysate in the peritoneal cavity throughout the dialysis session. Three litres of fluid are introduced first time, then every time two litres are exchanged leaving always 3 litres in the abdomen.

Indications for PD:

Because it provides the best rehabilitation potential as it is safe and easy, it is used for all ages and all sizes of patients with end stage renal failure.

Specific Indications for Peritoneal Dialysis include the following:

1 Infant and very young children.

2 End stage renal failure patients with cardiovascular or haemodynamic instability.

3 Hemodialysis patients with vascular access failure (especially diabetics).

4 Patients for whom vascular access can not be created (especially diabetics).

5 High risk of anticoagulants.

6 Patients who desire greater freedom to travel.

Contraindications:

Absolute:

- Extensive peritoneal fibrosis.
- Pleuroperitoneal leak.

Relative:

- The same as those in hemodialysis.
- Presence of colostomy or nephrostomy.
- Recent thoracic or abdominal surgery.
- Inguinal or abdominal hernia.
- Blindness.
- Mental retardation.
- Poor motivation and compliance.

Advantages:

- Ease of performance.
- High safety margin.
- Portability.
- Fewer dialysis-related symptoms.
- No routine anticoagulation.
- Better control of PTH levels.
- More liberal diet.
- Fewer medications.
- No viral transmission.

• Used safely in hemodialysis unstable patients and those with difficult vascular access.

Disadvantages:

• Low efficiency
• Body image problem because of the catheter
• Potential protein loss
• Potential infection
• Hypertriglyceridaemia.

Complications:

Mechanical:

• Pain during inflow owing to hot dialysate or rapid jetting.
• Pain during outflow due to ball-valve effect.
• Outflow failure due to constipation, obstruction or malposition of the catheter.
• Pericatheter leakage because of very early usage of the catheter.
• Scrotal oedema.
• Intestinal perforation.
• Cuff catheter erosion.

Cardiovascular:

• Fluid overload.
• Hypertension.
• Hypotension.
• Dysrhythmias.

Pulmonary:

• Atelectasis.
• Hydrothorax.
• Restricted chest movement.

Neurologic:

• Seizures and disequilibrium syndrome which are rare in comparison to hemodialysis.

Metabolic:

- Hyperglycaemia.
- Hyperlipidaemia
- Hyper or hypokalaemia.
- Hyper or hyponatraemia.
- Metabolic alkalosis.
- Protein depletion.
- Obesity**.**

Infectious and Inflammatory:

- Peritonitis.
- Exit site infection.
- Tunnel infection.

Peritonitis:

The incidence of peritonitis among PD patients is one episode every 12-18 months/patient.

Diagnosis:

- Cloudy outflow.
- Fever.
- Abdominal pain and bowel symptoms (e.g., cramps, diarrhea or constipation).
- Peritoneal fluid WBCs >100 ml with >50 % polymorphonuclear leucocytes.

Etiology:

- Gram +ve organisms account for 65-75 %.
- Gram -ve organisms account for 25-30%.

Treatment: Aggressive antibiotics.

Tunnel infection:

- This manifests as swelling, tenderness, redness & hotness.
- This is a dangerous form of infection, and if persists dispite taking proper antibiotics, the catheter should be removed.

KIDNEY TRANSPLANTATION

Definition:

Kidney transplantation means the treatment of chronic renal failure by surgical implantation of a kidney that is obtained from either healthy kidney donor or brain stem dead cadaver.

Principle:

- Kidney transplantation is performed by doing a unilateral nephrectomy for the donor to be implanted into the patient with end stage renal disease “The recipient”.
- The new kidney is placed in the patient's abdomen, usually in the right iliac fossa. The artery and vein are anastomosed to patient's vessels (usually internal iliac) and the ureter is implanted into the bladder. Kidney transplant in recipient's right iliac fossa with native kidney left in place.
- The native kidneys are left in place, unless there is an indication to be removed, e.g., uncontrollable hypertension, infection or if they are hugely enlarged.
- The immune system of the recipient considers the transplanted kidney as a foreign body and tries to destruct it.

Indications:

Patients with end stage renal failure requiring renal replacement therapy.

Contraindications:

1 Patient refusal.
2 Psychosis.
3 Age more than 60 years (relative).
4 Recurrent disease, if the original kidney disease that caused renal failure can recur in the transplanted kidney and destroy it, e.g., oxalosis.
5 Systemic disease: Some co-existing systemic diseases may contraindicate transplantation because of their effect on the patient's survival or because of the danger of post transplant immunosuppression therapy. These include the following:

- Severe respiratory disease, e.g., COPD.
- Severe cardiovascular disease, e.g., severe left ventricular failure.
- Severe hepatic disease, e.g., liver cirrhosis.
- Central nervous system, e.g., cerebral hemorrhage.
- Active peptic ulceration.
- Malignancy.
- Active infection.

6 Unrepairable urologic abnormalities.

Types of Kidney Donors:

1 **Living Donors:**

a) Blood related donors: one of the relatives of the recipient.

b) Unrelated donors: ethically, the emotionally motivated donors such as patient's partner rather than the

commercially motivated donors should be accepted as kidney donor.

2 **Cadaveric donors:**

These are persons with brain stem death but still with functioning cardiovascular and respiratory system. Cadavers are optimal kidney donors.

Immunological Assessment of Donor and Recipient Before Transplantation:

In order to prevent or minimize rejections after kidney transplantation, a number of immunological tests are done for both donor and recipient to be sure that they have identical tissue typing or at least with satisfactory similarity. These tests are:

1 **ABO blood grouping:**

Follows the same rules for blood transfusion

2 **Cross Matching:**

• Donor's leucocytes are mixed with the recipient's serum.

• The test is considered -ve and donor is suitable if none of donor's leucocytes was destroyed.

3 **HLA Typing:**

• The HLA system is a group of antigens present on the surface of all nucleated cells in the body.

• This system is responsible for recognition of immune system to "self cells" and "foreign cells".

• It is the major determining factor for graft rejection.

• The more similar the HLA system of recipient and donor, the less the incidence of post transplant rejection.

Contraindications for Donation:

A Living Donors:

1 Donor refusal.

2 Psychosis.

3 Age below 21 and above 60 years.

4 Renal disease.

5 Family history of hereditary renal disease (e.g., polycystic kidney disease).

6 Associated medical diseases:

- Cardiovascular: (e.g., heart failure, hypertension).
- Respiratory: (e.g., COPD).
- Hepatic: (e.g., liver cirrhosis, hepatitis).
- C.N.S.
- Metabolic (e.g., diabetes mellitus).
- Malignancy.
- Infections.

B Cadaveric Donors:

1 Absence of consent before death.

2 Age less than 3 or more than 70 years .

3 Renal disease.

4 Associated medical diseases: (vide supra).

Immunosuppression after Transplantation:

Definition: Immunosuppression therapy is used after kidney transplantation in order to modify the recipients immune system so that rejection is prevented.

Duration: Immunosuppression therapy continues for life.

Mode of Action:

• Immunosuppression can be achieved by different drugs.

• Each drug has a different mechanism by which it can depress leukocytes which are responsible for the immune response.

Regimens:

• Many regimens are present.

• Steroids are the corner stone drug used.

• Triple regimen (steroids-azathioprine-cyclosporine) is the commonest regimen.

• Other new drugs: (FK-506, Mycophenolate and Rapamycin).

• Polyclonal antibodies as ATG and ALG.

• Monoclonal antibodies as OKT3.

• Cymeric and humanized antibodies as simulect (Novartis) and zenapax (Roche).

Complications after KidneyTtransplantation:

Rejections:

• **Hyperacute:** Usually occurs immediately after surgery.

• **Acute:** Usually occurs a few days or weeks to months after surgery.

• **Chronic:** Usually occurs months to years after surgery.

Complications of Immunosuppression Therapy:

1 **General complications:**

• Infection.

• Increased incidence of malignancy.

2 Complications due to individual drugs:

• Steroids: hypertension, DM, atherosclerosis, Bone disease, GIT bleeding and cataract.

• Azathioprine: Bone marrow depression and hepatic dysfunction.

• Cyclosporine: Nephrotoxicity, hepatotoxicity, hypertension and DM.

Transplantation Versus Dialysis:

Advantages of Transplantation Over Dialysis:

1 Better quality of life:

• Independence from machine

• Correction of manifestations of chronic renal failure that are not corrected properly by dialysis such as anemia, bone disease, growth retardation in children, fertility and child bearing in adults.

• More ability to work.

2 Avoidance of diseases that may be transmitted through dialysis such as HIV and hepatitis.

3 Less cost than dialysis.

Disadvantages of Transplantation:

1 Complications of immunosuppression.

2 The possibility of graft loss.

3 The need for kidney donors.

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CONTENTS

Електронне навчальне видання

Моісеєнко Ірина Олегівна,
Псарьова Валентина Григорівна,
Приступа Людмила Никодимівна та ін.

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