Acute Renal Failure

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Introduction

Acute renal failure (ARF) is a common clinical syndrome characterized by an abrupt deterioration in kidney function resulting in abnormalities in volume-regulatory, metabolic-regulatory, excretory, and endocrine functions. At presentation, ARF is roughly evenly divided between patients who are oliguric (produce < 400 mL/day urine output) and those who are nonoliguric (produce > 400 mL/day urine output). Most clinicians would accept a rise in the serum creatinine concentration of > 0.5 mg/dL/day and a rise in the blood urea nitrogen (BUN) level of > 10 mg/dL/day over several days as diagnostic of ARF. Many definitions can and have been proposed for ARF. In one review of 28 different studies, no two used the same diagnostic criteria [47]. It is not clear, in fact, whether an optimal definition exists. The syndrome of ARF has multiple causes, diverse manifestations, and a clinical presentation covering a continuum from mild to life-threatening disease. A patient may progress from normal renal function to dialysis-dependent ARF within a few days.

ARF may evolve from diminished renal blood flow (RBF), termed prerenal functional ARF; from an acute severe parenchymal insult, termed intranenal structural ARF; or from obstruction to urine flow termed postrenal obstructive ARF. Intrarenal ARF is further characterized according to the site of injury as a primarily vascular, glomerular, tubular, or interstitial process. The relative contributions of different etiologies to the development of ARF vary between community-based and hospital-based populations; and within the hospital, between medical intensive care unit, surgical intensive care unit, and nonintensive care unit populations. Prerenal azotemia, for instance, accounts for some 70% of community-acquired and 40% of hospital-acquired ARF. Intrarenal causes account for at least 50% of hospital-acquired ARF but are less common in community-acquired cases.

ARF is present on admission to hospital in 1% of cases and further complicates up to 5% of admissions. The mean age of affected individuals has increased such that 36% of patients in one recent hospital survey were > 70 years old at presentation [37]. Despite decades of improvements in the provision of intensive care and specifically in the provision of renal replacement therapy, the morbidity and mortality associated with ARF remains extremely high. The percentage of patients with ARF requiring dialytic intervention ranges from 20 – 60%. Of those requiring dialysis who survive, 12 – 33% have been reported to require long-term renal replacement. The mortality in dialysis-requiring ARF is generally reported to be ≥ 50%, while the mortality in those admitted to the hospital with prerenal azotemia is approximately 7%. For example, a recent cohort analytic study reported mortality rates of 62%, 31%, and 7% in matched groups who developed dialysis-requiring, nondialysis-requiring, or no ARF, following a contrast procedure [36]. A mortality rate of 63.7% was noted in those with

dialysis-requiring ARF vs. 4.3% in those without ARF in a prospective cohort study of 43,642 patients after open cardiac surgery [7].

The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) reported a median duration of survival for a group of 490 seriously ill patients with dialysis-requiring ARF of only 32 days [28]. Only 27% of patients in this report were alive after 6 months, but of those who survived 62% rated their quality of life as good. The overall estimated cost (in 1994 US dollars) per quality-adjusted life year saved by initiating dialysis and continuing aggressive care in this group of patients was $128,200. When the patients were stratified into prognostic categories, the estimated cost per quality-adjusted life year saved was $274,100 vs. $61,900 for those in the worst and best prognostic categories, respectively.

ARF is a serious, common, complicated, and costly medical illness.

Approach to the Differential Diagnosis of ARF

General Comments

There is often more than one contributing etiologic factor in an ARF presentation, and a broad consideration of all possible causes is necessary. The time-honored approach to establishing a diagnosis in renal disease rests on 1) localizing the predominant site(s) of renal injury and 2) establishing the temporal course of the event(s) leading to the presentation. If the process is localized to prerenal or postrenal sites, the treatment required is restoration of normal perfusion or relief of obstruction, and, notwithstanding the recognition that there are many causes of pre- and postrenal ARF, the specific diagnosis is often easily made. In intrarenal ARF (be it primarily due to vascular, glomerular, tubular, or interstitial processes), specific treatments are less readily available and recovery of renal function in those who survive is slower and less certain.

An elevation in BUN and creatinine may be acute, acute on chronic, or chronic. In a patient with recently measured and available BUN and creatinine levels, determining which is the case may be easy, e.g. a patient who develops ARF as an iatrogenic complication during a hospital admission. However, the distinction must be made in all cases because a delay in the diagnosis and treatment of acute (or acute on chronic) renal failure may allow a prerenal syndrome to progress to established acute tubular necrosis (ATN), a potentially treatable intrinsic renal process such as renal vasculitis to progress to ESRD, or a potentially life-threatening metabolic complication to develop in any patient with deteriorating renal function. Features that suggest chronicity are summarized in Table 1. Most of these are nonspecific. If doubt exists as to the nature of the temporal onset of the renal failure, then it should be treated as acute until proven otherwise.

Prerenal Functional Azotemia

Prerenal azotemia results from a persistent, significant decline in renal blood flow (RBF) that overcomes autoregulatory mechanisms producing a reduction in glomerular filtration rate (GFR) and hence a rise in BUN and serum creatinine concentrations. Implicit in the functional component of the definition is that complete reversibility of prerenal ARF occurs with restoration of RBF. Often more than one

Table 1. Factors Suggestive of Chronicity*

History
- Prior diagnosis of renal impairment
- Remote / Prolonged history of proteinuria or hematuria
- Family history of hereditary renal disease (i.e. ADPKD)
- Long history of systemic illness
- Long duration/evolution of presenting symptoms

Physical Examination
- Ballotable polycystic kidneys

Urinalysis
- Broad casts

Laboratory Tests
- Anemia of chronic disease
- Percent carbamylated hemoglobin

Radiology
- Small kidneys

*Unless there is clear historical evidence indicating chronic renal failure or bilateral small scarred kidneys renal failure should be treated as acute until proven otherwise.

etiologic factor will be present. The causes of prerenal azotemia are listed in Table 2. Medications that interfere with autoregulatory mechanisms in the kidney are included in the list. A nonlinear relationship exists between serum creatinine concentration and GFR. As a result, individuals with chronic renal insufficiency exposed to prerenal insults are susceptible to more dramatic increases in BUN and serum creatinine concentrations. In chronic renal failure, prerenal effects are common and should be considered before activity or progression of the primary renal disease is invoked to explain a rise in BUN and creatinine.

A careful history for gastrointestinal, skin, and renal salt and water losses, or for bleeding is important. The symptoms of thirst or orthostatic dizziness may be important diagnostic clues. A complete history of drug ingestion, including prescription and nonprescription medications, is often instructive. Symptoms indicating other underlying etiologies may be apparent in the presenting complaint and should be sought in a thorough systems review. Physical exam needs to be complete. The history may direct a search for signs of chronic liver disease, congestive heart failure (CHF) or other specific etiologies. An assessment of intravascular volume status is always necessary. This should include a search for orthostatic hypotension and tachycardia and assessment of jugular venous pressure, skin turgor, and moistness of mucous membranes. (Table 3).

Jugular venous pressure can be measured with the patient reclined at any angle, as the vertical distance separating two imaginary horizontal lines that correspond respectively to the level of the manubriosternal angle and top of the neck vein pulsation (assuming the top of the venous pulsation in the neck is visible). In the envolemic state, when the head of a patient's bed is elevated to a 45° angle, neck vein pulsation is just visible at the root of the neck. Likewise, in this position an external jugular vein allowed to fill from above by occlusive external compression at the root of the neck will empty briskly with release of occlusive pressure. However, when intravascular volume is low, even with the patient lying perfectly flat, neck vein pulsation may be absent, and an external jugular vein allowed to fill from above by external compression will continue to empty briskly when the compression is removed.

Postrenal Obstructive ARF (Chapter I-14)

Common causes of ARF from obstruction include benign prostatic hypertrophy or prostatic carcinoma in men leading to obstruction of the bladder outlet; carcinoma of the uterine cervix in women leading to either obstruction

Table 2. Etiology of Acute Renal Failure

ARF → Anuric:
- Bilateral renovascular occlusion
- Severe acute glomerulonephritis
- Acute cortical necrosis
- Bilateral ureteric obstruction
- Bladder outflow obstruction

↓ *Oliguric/Non Oliguric:

Prerenal "functional" ARF	*Intrarenal "structural" ARF*	*Postrenal "obstructive" ARF*
Hypotension	*Tubular*	*Intrarenal*
Volume Depletion	Ischemic ATN	Acute uric acid nephropathy
Extrarenal sodium loss	Any of the causes of prerenal ARF	Etylene glycol poisoning
Gastrointestinal losses	Nephrotoxic ATN	Drugs (methotrexate, acyclovir, sulfonamides, gallium nitrate)
Vomiting, Diarrhea,	Antibiotics (aminoglycosides, amphotericin B...)	*Extrarenal (chapter I-14)*
Fistulae, Bleeding	Heavy metals (cisplatin)	
Skin losses	Anti-cancer drugs (ifosfamide)	
Burns, Heat exposure	Immunosuppressives (cyclosporine, FK506)	
Intrarenal sodium loss	Radiocontrast agents	
Mineralocorticoid deficiency	Endogenous toxins (myoglobin, light chains, hemoglobin)	
Diuretic exposure	*Acute tubulointerstitial nephritis*	
Osmotic diuresis (hyperglycemia, uremia, mannitol)	*Vascular*	
Salt-wasting nephropathy	Atheroembolic disease	
Third-Space fluid sequestration	Small vessel vasculitis	
Cirrhosis,CHF,	Malignant hypertension	
Nephrotic syndrome	Scleroderma renal crisis	
Pancreatitis, Crush injury,	Thrombotic microangiopathies	
Other ...	*Acute glomerulonephritis*	
Hepatorenal syndrome		
Drug-related		
Nonsteroidal antlinflammatory drugs		
ACE inhibitors		
Amphotericin B		
Cyclosporine / FK506		
Interleukin 2		

*Always consider possibility of multiple coexisting etiologies

of the bladder outlet or ureter bilaterally; and a blocked Foley catheter in hospitalized patients. Other pelvic or retroperitoneal tumors may also cause obstruction. A blood clot, stone, or tumor within the lumen of the lower urinary tract in the bladder, ureter bilaterally, or single ureter in the case of a transplanted or a solitary native kidney, can produce a similar result. Neurogenic bladder is also a common finding, especially in diabetic patients. Drugs with anticholinergic side effects or the postoperative state may precipitate urinary retention in predisposed individuals. Intrarenal obstruction due to precipitation of crystals within the tubules is rare. It is considered here in the differential diagnosis, although this

Table 3. An Approach to the Differential Diagnosis of ARF

ARF Evaluation
↓

Steps: 1-2 History and Physical Exam ↓	→	3 List Plausible Contributing Factors	→	4-5 Urinalysis and Diagnostic Indices (interpret in context of 1-3)	→	6 Decide on Probable Cause(s) (consider coexisting etiologies)	→	7 Confirmatory Tests (as/if needed)

	Prerenal ARF	*Intrarenal ARF*	*Postrenal ARF*
1. History	Thirst Orthostatic Symptoms Weight loss Vomiting, Diarrhea, Hematemesis,Melena Diuretic use, Polyuria Exposure to certain drugs Disease specific symptoms for CHF, Cirrhosis	Likely Ischemic ATN Hypotension or shock Prolonged/severe prerenal symptoms Nephrotoxic Exposure Radiocontrast, Recent medications, Bone pain Likely pigment exposure: Excessive exercise, Seizures, Excess alcohol ingestion, Physical injury Tubulointerstial /Vascular/ Glomerular Rash, Arthralgias, Fever Angiography, Vascular surgery Strep infection, Hemoptysis, Intravenous drug abuse	Extrarenal Frequency, Nocturia, Hesitancy, Poor stream, Post-void dribbling, Double micturition, Incontinence Hematuria, Colic, Suprapubic/ flank pain Diabetic neuropathy,Anti-cholinergic drug exposure Postoperative patient Intrarenal Drug exposure Intoxication
2. Physical Examination	Orthostatic tachycardia and hypotension Decreased jugular venous pressure, Reduced skin turgor, Dry mucous membranes Disease specific signs: e.g. Displaced apex, Gallup rhythm, Rales, Parasternal heave, JVD, Hepatomegaly, Ascites, Edema in CHF; ...	Signs of prerenal disease Muscle tenderness Maculopapular rash Palpable purpuric rash, Livedo reticularis Digital infarcts, Retinal “cholesterol” embolus New murmur, Extracardiac signs of endocarditis	Bladder distension by palpation or percussion Enlarged prostate Palpable pelvic mass on internal examination
3. List Plausible Diagnoses (Table 2)	Prerenal Causes ...	Intrarenal Causes...	Postrenal Causes...

Table 3. Continuation

	Prerenal ARF	*Intrarenal ARF*		*Postrenal ARF*	
4. Urinalysis	Typical ‘‘bland" S.G. > 1.018, Neg/Tr Protein Neg heme Cells: none Casts: hyaline Atypical “Active” Additional/ other etiology likely	Typical “active” S.G. 1.010, 1+ to 3+ Protein Heme + or - Cells & Casts: RBC, WBC, Tubular epithelial cells free or in casts, granular casts	Atypical “bland” Other etiology likely	Typical S.G. > 1.010, Neg/1+Protein Heme – or + Cells & Casts: None or RBCs or WBCs, possible but tubular epithelial in cells and cellular or granular casts not expected	Atypical proteinuria or non- hyaline casts suggest intrarenal cause
5. Diagnostic Indices	Typical (any cause) FE_{Na} < 1% Urine sodium < 20 mM But Fe_{Na} > 1% or Urine sodium > 20 mEq/1 Can be seen with diuretic use, preexisting chronic renal failure, salt wasting nephropathy, and/or a non prerenal etiology	Typical (any cause of ATN) FENa < 1% Urine sodium > 20 mEqA But FeNa < 1% or Urine sodium < 20 mM Can be seen with Radiocontrast exposure Pigment exposure Advanced liver disease Early measurement in Interstitial nephritis Acute GN Coexisting prerenal state		Generally not useful in the diagnosis of postrenal ARF	
6. Decide on probable cause / causes & 7. Order confirmatory tests as indicated					

syndrome is not truly postrenal. Causes of intrarenal obstruction include acute uric acid nephropathy, ethylene glycol toxicity complicated by calcium oxalate precipitation, and drugs such as methotrexate, acyclovir, and sulfonamides.

A detailed history, including a drug history, may suggest obstructive ARF. Complete anuria in ARF is rare and generally narrows the differential diagnosis to an obstructive etiology, renovascular occlusive etiology, severe acute glomerulonephritis, or a catastrophic ischemic event such as acute major bleeding – as described in obstetric cases of acute cortical necrosis (Table 2). However, the urine output is a poor indicator of underlying obstructive problems because polyuria, alternating oliguria and polyuria, anuria, or an

apparently normal urine output may all be seen. Specific symptom complexes may point to prostatic disease, bladder outlet obstruction, or stone disease. The physical exam should assess for a distended bladder, a pelvic mass, and an enlarged prostate. When bladder distension is suspected, measurement of a postvoid residual volume by straight catheterization is diagnostically helpful.

Intrarenal Structural ARF

The causes of intrarenal ARF (Table 2) are grouped into categories based on localization of the dominant injury. Tubular pathology defining the clinical syndrome of ATN accounts for the majority of the cases of intrarenal ARF. ATN is the result of either ischemic or nephrotoxic tubular injury. Ischemic ATN and prerenal azotemia are at opposite poles of a continuum of renal injury resulting from hypoperfusion. A prerenal azotemic state left untreated may progress towards established ATN. Toxic and drug-related causes of ATN are listed separately (Table 6). Acute tubulointerstitial nephritis may account for approximately 10% of cases of intrarenal ARF, and may be idiopathic or more often secondary to drugs, toxins, autoimmune, idiopathic, or infective processes. Among the vascular causes, atheroembolic disease is suggested to be underrecognized as a factor in ARF presentations [41]. It may occur spontaneously or as a complication of cardiac catheterization, vascular, and cardiac surgical procedures (Part I, Chapter 6). Glomerular diseases account for about 5% of intrarenal ARF and include, in addition to vasculitic syndromes, all other causes of rapidly progressive glomerulonephritis (RPGN).

A history of systemic disease, fever, chills, IV drug use, arthralgia, skin rash, recent infection, sinusitis, hemoptysis, hematuria, or recent drug exposure may point towards glomerular or interstitial pathologies. Recent exposure to exogenous toxins or a history of immobilization, seizure, skeletal muscle injury, or ethanol intoxication may point towards a nephrotoxic etiology. Clues from the physical examination may include acrocyanosis, digital infarction, livedo reticulosis or funduscopic evidence of cholesterol emboli in atheroembolic disease; skin rash or palpable purpura in vasculitis; petechia and nonpalpable purpura in hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP); sclerodactylia in systemic sclerosis; a new murmur, fever, splinter hemorrhages, Osler's nodes, Janeway lesions, or Roth spots in infective endocarditis; a maculopapular erythematous rash in allergic interstitial nephritis; and muscle tenderness in rhabdomyolysis.

Urinalysis and Diagnostic Indices in the Differential Diagnosis of ARF

Urinalysis should be performed in all cases and should include, at the very least, reagent strip testing and microscopy of a freshly-spun sediment. Measurement of urinary biochemical indices may provide additional information. Urinalysis data are interpreted in the context of the clinical situation in which they are obtained. Specifically, the urinalysis is used to aid localization of and differentiation between likely causes of ARF (Table 3). In essence, one interrogates the ability of the glomeruli and tubules to elaborate urine appropriately. From this, one attempts to derive an indication of nephron structural and functional integrity.

Red cells, not normally present in the urine, can enter the urinary tract anywhere from the glomerulus to the tip of the urethra. In prerenal disease, they are unexpected unless sec-

ondary to traumatic catheterization. In postrenal disease, they may reflect underlying pathology in the lower urinary tract. If present in the form of casts, however, they are indicative of intrarenal disease and almost always a glomerulopathy. The presence of detectable heme pigment in the absence of microscopic hematuria points towards a rhabdomyolytic or hemoglobinuric pigment-induced ARF.

White cells also may arise from anywhere along the urinary tract, from the glomerulus to the tip of the urethra. The common thought to consider them only indicative of a lower UTI (a common etiology of leukocyturia) needs to be guarded against in ARF patients. Intrarenal inflammation or infection also need to be considered. Again, the presence of white cell casts or white cells in the company of granular casts or significant proteinuria heralds an intrarenal cause. Possibilities include interstitial nephritis, acute glomerulonephritis, and pyelonephritis.

Tubular epithelial cells (present < 1 per several high-powered fields in normal urine) are frequently seen in intrarenal ARF. Intact cells may be seen free or within tubular epithelial cell casts or degraded as constituents of the granular casts. Muddy-brown granular casts are particularly classical for acute tubular necrosis.

Large quantities of protein are indicative of intrarenal disease, while trace to 1+ proteinuria may be present in the concentrated urine of prerenal azotemia or sometimes in postrenal azotemia. Quantitatively, in an adult > 2g of proteinuria in 24 hours, or a urine protein to creatinine ratio > 2, is suggestive of underlying glomerular disease (nephrotic range proteinuria > 3.5g/1.72m^2/day is pathognomonic of glomerular disease). Tubular disease typically is associated with < 2g (urine protein to creatinine ratio < 2) per 24 hours of proteinuria. Qualitatively, glomerular and tubular proteinuria are distinguished based on size and charge characteristics by urine protein electrophoresis. Leakage of larger molecular weight proteins is associated with glomerular disease. The predominantly positively-charged immunoglobulin light chains responsible for nephrotoxic ATN in multiple myeloma are characteristically missed by reagent tests, which preferentially detect anionic (negatively-charged) proteins. Gram quantities of Bence-Jones proteinuria may be present with a negative urine dipstick for protein and must always be sought for directly in adult patients with unexplained renal failure.

Diagnostic indices reflecting the tubular capacity to handle solutes and water help differentiate prerenal azotemia from ischemic ATN. The context in which the measurements are taken determines the expected results. In general, if a state of absolute or relative decreased effective arterial volume is present, then, in the absence of pharmacologic inhibition, healthy kidney tubules should maximally reabsorb solutes and water. Whereas in prerenal azotemia this should be possible, in ATN maximal reabsorptive capacities are reduced. Diagnostic indices provide corroborative evidence for suspected diagnoses. It should be recognized, however, that they may be misleading, if interpreted in isolation, without regard for the entire clinical context.

The reabsorption of water is dependent on tubular integrity, antidiuretic hormone (ADH), and the maintenance of the medullary hypertonicity concentration gradient. In respect of ADH secretion, protection of volume will take precedence over protection of osmolality. A concentrated urine with an increased urine osmolality and an increased urine creatinine to plasma creatinine ratio is expected in prerenal disease vs. ATN. As shown in Figure 1, the absolute discriminating value of these 2 indices of water reabsorption with respect to prerenal azotemia in ATN is poor, with considerable overlap.

Overlap between diagnostic indices in prerenal azotemia and ATN exists when solute reabsorption in the form of urea nitrogen is considered. As opposed to creatinine, urea nitrogen is significantly reabsorbed by healthy tubules, and more avidly so when the kidney is underperfused. The BUN to serum creatinine ratio describes this difference. Attempts to separate prerenal disease and ATN based on this ratio have suggested that a BUN to serum creatinine ratio > 20:1 is indicative of prerenal disease. However, BUN concentrations and creatinine concentrations are both subject to many influences independent of the state of renal perfusion and tubular integrity.

Urine sodium concentration is also frequently measured in an effort to differentiate between prerenal azotemia and ischemic ATN. A urine sodium < 20 mM is suggestive of prerenal disease, while one > 40 mM is suggestive of ATN. Overlap persists between these 2 syndromes in terms of urine sodium concentration, and additional factors can impact urine sodium concentrations (Table 3). Perhaps the most frequently used diagnostic index is the fractional excretion of sodium (FE_{Na}). It is derived from the urine-to-plasma sodium ratio divided by the urine-to-plasma creatinine ratio, multiplied by 100, and is expressed as a percentage (Figure 1). It is therefore an integrated index describing the extraction of sodium and water from the glomerular filtrate. FE_{NA} is the most sensitive index to differentiate pre- vs. intrarenal disease: an FE_{Na} < 1% suggests prerenal disease, while an FE_{Na} > 1% suggests ATN. However, nonazotemic patients in sodium balance will often have an FE_{Na} of < 1%, because the amount of sodium reabsorbed to maintain homeostasis (in those on a normal salt diet) is typically > 99% of the sodium filtered. Similarly, an FE_{Na} of < 1% in ARF has been described in intrarenal and postrenal disease and an elevated FE_{Na} is occasionally seen with prerenal disease [61] (Table 3).

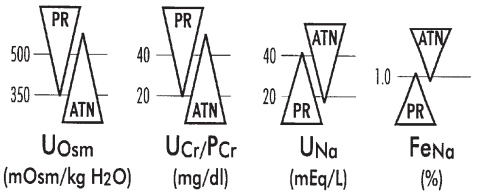

Figure 1. Diagnostic indices in acute renal failure. The horizontal axis displays four laboratory tests and the units used to differentiate functional prerenal (PR) azotemia from acute tubular necrosis (ATN). The vertical axis depicts values that define the nondiagnostic zones of overlap between the designated values and diagnostic areas of nonoverlap above and below the designated values. The derived urinary index, the fractional excretion of sodium (FE_{Na}), has essentially no nondiagnostic overlap zone (exceptions discussed in text). The fraction of the filtered sodium FE_{Na} can be calculated from a urine specimen:

$$FE_{Na}(\%) = \frac{\text{quantity of sodium excreted}}{\text{quantity of sodium filtered}} \times 100$$

Because the quantity of sodium excreted is equal to the product of the urine sodium concentration (U_{Na}) and the urine volume (V); the quantity of sodium filtered is equal to the product of the plasma sodium concentration (P_{Na}) and the GFR (or creatinine clearance, $C_{Cr} = U_{Cr} \times V/P_{Cr}$):

$$FE_{Na}(\%) = \frac{U_{Na} \times V}{P_{Na} \times (U_{Cr} V / P_{Cr})} \times 100 = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$$

[Kelley WN (ed) 1997 Internal Medicine. Lippincott-Raven, Philadelphia, 934]

Confirmatory Tests in the Differential Diagnosis of ARF

Specific additional tests useful in the differential diagnosis of ARF are shown in Table 4. Among these, renal ultrasound is often used to evaluate for a postrenal cause of ARF. It is usually diagnostic in this setting, although bilateral pelvicaliectasis may not have had time to develop in acute obstruction, and in rare conditions the lower urinary tract is encased and nondistensible, as can occur in retroperitoneal fibrosis. Ultrasound also confirms the presence of two kidneys and pro-

Table 4. Specific / Confirmatory Tests in the Approach to the Differential Diagnosis of ARF

Prerenal ARF
Response to restoration of intravascular volume
or reduction/cessation of drug-related factor
Investigation of underlying disease state
e.g. liver evaluation, cardiac evaluation,
ACTH stimulation fest
Intrarenal ARF
Ischemic ATN: Workup of unexplained hypotension as indicated
Drug-related ATN: Monitoring serum drug levels
Multiple myeloma: serum protein electrophoresis and urine immunoelectrophoresis, skeletal survey, bone marrow aspirate, +/- kidney biopsy
Rhabdomyolysis: CK and aldolase concentrations
Hemolysis: haptoglobin, free serum and urine hemoglobin estimation, LDH level, direct antiglobulin test
Acute tubulointerstitial nephritis: Serum and urine eosinophils, kidney biopsy
Atheroembolic Disease: LDH, C3/CH50 complement, absolute eosinophil count
Thrombotic microangiopathy: stool cultures for VTEC, LDH, platelet count, reticulcyte count, haptoglobin
Vasculitis and/or glomerulonephritis: quantitation of urinary protein excretion, ANCA, ANA, anti-GBM antibody, C3, C4 and total complements, ASO titer, hepatitic serologies, kidney biopsy
Postrenal ARF
Renal ultrasound
Other noninvasive / invasive procedures as required
Measurement of post-void residual volume

ACTH: adrenocorticotropic hormone, ANCA: antineutrophil cytoplasmic autoantibody, ANA: antinuclear antibody, CK: creatine kinase, LDH: lactate dehydrogenase, VTEC: verotoxigenic E. coli, GBM: glomerular basement, ASO: antistreptolysin O

vides a measure of renal size, useful in the distinction between chronic and acute disease (Table 1). Doppler ultrasound provides information regarding perfusion and resistive indices. The resistive index is derived from dividing the peak systolic excursion on Doppler waveform analysis by the peak systolic minus the peak diastolic excursion. In a nonspecific manner, the resistive index approaches unity with various pathological conditions that perturb diastolic arterial flow to a greater extent than systolic arterial flow. In general, interstitial swelling or obstruction may produce such an effect. In studies of normal kidneys, the probability that a single measurement of the resistive index is > 0.7 was estimated to be 6%, while the probability that an average of 3 readings is > 0.7 was estimated to be 3% [32]. Therefore, a resistive index > 0.7 should raise suspicions for an underlying abnormality.

Summary

Table 3 details a stepwise approach to the evaluation of ARF. ARF is a complex disorder and several contributing factors may play a role in the same case. A careful history and physical examination will generate a list of plausible causes, and is complemented by a skillful interpretation of urinalysis and appropriate laboratory and radiologic investiga-

tions. This approach will lead to the correct diagnoses in most cases. If the case does not fit comfortably into the categories of prerenal and postrenal disease or ATN, then resolution of the diagnostic dilemma will generally require a renal biopsy. Failure to do this could lead to missing treatable diseases [51].

Pathophysiological Mechanisms in ARF

This section deals specifically with pathologic mechanisms that relate to the development of ischemic or nephrotoxic ATN. Significant progress has been made in unraveling the multiple, synergistic, and interdependent mechanisms involved in generating ATN. The term ATN is somewhat a misnomer because renal failure in this syndrome produces typically only patchy segmental necrosis in the tubules, *but* it appropriately directs attention on tubular injury as the focal point for understanding the pathogenesis. The clinical course of ATN can be considered in terms of 3 phases: an initiation phase, a maintenance phase (where the triggering factors of ARF have ceased to exist, but the renal failure continues), and a recovery phase. In the clinical setting, these phases may overlap, although ongoing triggering events may hamper ongoing recovery. These events will be discussed separately.

Initiation Phase – Hemodynamic Alterations [45]

Any cause of a significant decline in absolute or relative effective arterial blood volume results in a decrease in perfusion of vital organs and a fall in mean arterial pressure. Both central and peripheral baroreceptors are activated to initiate neurohumoral compensatory mechanisms, including an increase in cardiac contractility and venous and arteriolar vasoconstriction, to improve the perfusion of vital organs and maintain blood pressure. A variety of vasoactive substances are released locally and systematically to promote arteriolar contraction, primarily in the renal, splanchnic, and musculocutaneous circulatory beds. In the kidney alterations in levels of angiotensin II (Ang II), endothelin, sympathetic amines and endothelial-derived relaxant factor are important. Initially, in response to a global reduction in RBF, preferential vasoconstriction of efferent postglomerular arterioles attempts to maintain glomerular perfusion pressure and GFR. Sustained significant reductions in RBF override this mechanism, however, and result in substantial declines in GFR. Contraction of glomerular mesangial cells in response to mediators of vasoconstriction may also contribute to the decrease in GFR by reducing the surface area for filtration.

Initiation Phase – Medullary Hypoxemia [4]

Normal renal physiology requires generation and maintenance of a medullary hypertonicity gradient. It is achieved via a countercurrent system of blood vessels and tubules in the renal medulla. As a direct consequence of countercurrent transport, oxygen levels in the medullary interstitium are decidedly low. Active transport processes in the straight segment of the proximal tubule (S3) and in the medullary thick ascending limb of the loop of Henle therefore take place in a zone of relative regional hypoperfusion and relative hypoxia – the outer medulla. The ATP-dependent ac-

tive transport processes dictate the demand for, while perfusion and blood oxygen content dictate the supply of, oxygen in a delicately balanced system. As RBF decreases, medullary hypoxemia can rapidly ensue. A variety of agents attempt to regulate oxygen homeostasis in these circumstances, including vasodilatory prostaglandins, nitric oxide, dopamine, and adenosine. A redistribution of blood flow may help, both by reducing GFR and therefore tubular workload, and by increasing oxygen delivery to the tubules. Some mediators may also directly inhibit transport processes and in this way further reduce tubular workload. However, as adaptive responses are overwhelmed, tubular injury inevitably ensues.

Initiation Phase – Tubular Injury

Nephrotoxic or ischemic insults can cause tubular injury. Insults may occur separately or in various combinations, e.g. the shocked patient on aminoglycoside antibiotics or the dehydrated patient with myeloma who receives an injection of radiocontrast. Nephrons are typically injured focally and segmentally. The injury may be lethal, resulting in necrosis or apoptosis, or it may be sublethal, resulting in structural and functional alterations that fall short of cell death. Overlap in the nephron segments affected by ischemia and nephrotoxins is possible, as is synergy in mediating damage, e.g. decreased RBF may lead to ischemic tubular injury in S3 segments, while also enhancing absorptive concentration of nephrotoxic antibiotics throughout the proximal convoluted tubule.

Initiation Phase – Consequences of Tubular Injury [38]

Tubular injury leads to an ATP-depleted state in tubular cells. Disruption of normal cytoskeleton, cell-cell contact at tight junctions, and loss of cell polarity with redistribution of Na-K-ATPase and other important proteins follows. At a biochemical level, cytosolic calcium levels rise and a variety of enzymes are abnormally activated. Ultrastructurally, cells appear swollen and microvilli are shed into the tubular lumen. Congestion of medullary capillaries is also a characteristic finding. Such alterations in the tubulointerstitial compartment leave it no longer adapted to water and solute transport or oxygen delivery, thus aggravating local ischemia and tubular injury. Some cells may suffer apoptosis or necrosis. A mixture of viable and nonviable cells is shed into the tubular lumen.

Accumulation of intraluminal debris and Tamm-Horsfall protein leads to intratubular obstruction. Impedance of urine flow in turn increases intraluminal and Bowman's capsular hydrostatic pressures, thus reducing GFR. In addition, transtubular backleak of filtrate occurs secondary to loss of cell-cell contact and sloughing of tubular cells. Hemodynamic alterations, intratubular obstruction, and transtubular backleak combine to produce the decline in GFR (Figure 2).

Maintenance Phase

The maintenance phase of ATN is characterized by persistence of renal failure, with GFR sometimes staying at its nadir for several weeks. Mechanisms thought to be responsible for sustained renal failure include toxic effects of reactive oxygen species generated as part of a reperfusion injury; persistent maladaptive

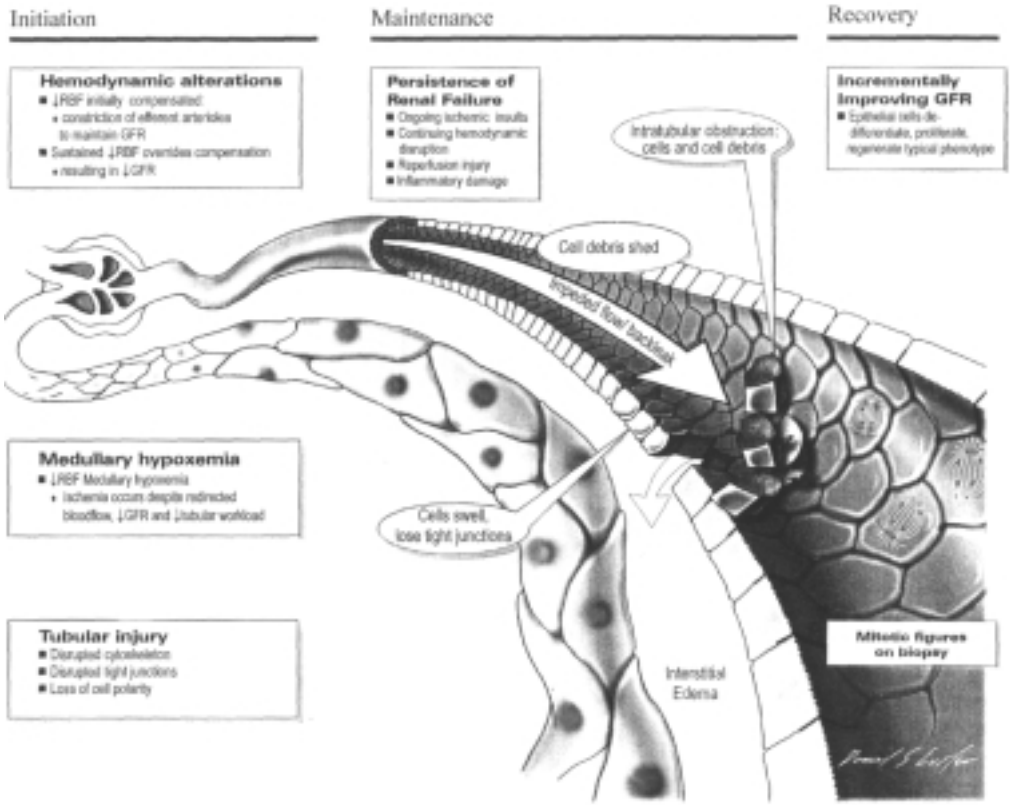

Figure 2. Mechanisms of reduced GFR in acute tubular necrosis.

intrarenal hemodynamic alterations; chemotaxis and adherence of neutrophils and platelets to intercellular adhesion molecules that have been unregulated on altered endothelial tissue; release by the leukocytic infiltrate of a mixture of damaging inflammatory mediators, proteases, elastases and other enzymes. Prolongation of ATN may also result from ongoing ischemic insults in dialysis-requiring ARF, due to inter- or intradialytic hypotensive episodes, combined with continued autoregulatory failure to maintain perfusion. The role of membrane biocompatibility in initiating inflammatory events that prolong ARF has received much attention recently. Finally, ongoing difficulties in maintaining adequate oxygen supply and in avoiding nephrotoxic exposures often complicate the course of a critically ill patient with ATN.

Recovery Phase

The recovery phase of ATN is characterized clinically by a diuresis followed by incremental improvements in GFR. At a cellular level, it is thought that some tubular epithelial cells dedifferentiate and recapitulate many of the processes involved in normal epithelial development in order to regenerate functionally intact tubules. Other cells may repair their cytoskeleton, cell-cell and cell-matrix interac-

tions and recover a normal functional phenotype. Mitotic figures are characteristically seen in biopsies at this time. The role of growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1) in regulating these processes is being investigated [35].

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 prerenal 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 [13]. As a result, there is a growing consensus (see comments published in JAMA regarding paper by Connors [13]) that the role of right heart catheterization needs to be studied by randomized clinical trials in those broad groups of patients for whom controversy 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 associated 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 [62].

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 [58]. 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. While uncontrolled data suggested a higher survival rate in patients who had an initial increase in urine output in response to furosemide, this observation was not upheld in controlled studies [11].

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 established ATN. To determine the utility of "low-dose" dopamine in preventing ATN, it has been estimated [17] 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 [39]. 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 [17]. A post-hoc 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 [8]. 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 [56]. 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, placebo-controlled 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 [1]. Disappointingly, as compared with placebo, anaritide (a synthetic form of ANP) had no significant effect overall on the key outcome measures of need for dialysis, the rate of dialysis-free survival 21 days after treatment, and overall mortality. In the anaritide group, however, the subgroup of patients with oliguria had a reduced need for dialysis during the first 14 days and greater dialysis-free survival at 21 days. This type of subgroup analysis is hypothesis generating but does not constitute proof of benefit. In the case of anaritide, a follow-up randomized study in oliguric ARF has been terminated early because of failure to detect any benefit [3]. It remains to be seen whether specific patient groups or clinical settings can be identified in which this new drug will confer benefit.

Calcium channel blockers have been used with some success in ameliorating renal insufficiency in the short term after renal transplantation [11]. 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 situations 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 insensible losses to maintain a euvolemic state is advised.

The general inability of the kidney in ATN to handle excess free water and elaborate a 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, intravenous 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, potassium-sparing 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 independently 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 administered phosphate binders. Infrequently, hyperphosphatemia is severe enough to raise the calcium-phosphate product to a point where dialysis is required to prevent metastatic calcification. Magnesium-containing 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 D_3 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 protein-energy malnutrition [30].

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.

Prescriptions can be based on Harris-Benedict and Long equations [59]. Caloric requirements of 30 – 35 kCal/kg/day and protein requirements of 1.5 g/kg/day are not unusual. Protein is generally provided as mixed essential and nonessential amino acids, and lipids are used to supply 30 – 40% of total daily calories. In studies where the normalized protein catabolic rate (nPCR) has been measured, it has been noted to frequently exceed 1.5 g/kg/day and to vary intra-individually from day to day. Nutritional prescriptions based on equations that predict protein requirements may fall short of providing sufficient protein. Aggressive hyperalimentation with amino acids in a setting complicated by decreased utilization may, on the other hand, simply fuel urea nitrogen generation. Is it possible in profoundly hypercatabolic patients to individualize nutritional prescriptions and successfully override utilization difficulties such that a net even or positive nitrogen balance is obtained? Would it be beneficial to do this? Should nutritional supplementation be titrated to the protein catabolic rate calculated from urea nitrogen generation or total nitrogen appearance? Would this provide for better outcomes? What is the role of recombinant human growth hormone or insulin-like growth factor-1(IGF-1) in promoting an anabolic state and better overall outcomes in ARF? Answers to these questions are not readily available.

Renal Replacement Therapy (RRT)

Traditional indications for initiation of renal replacement therapy (RRT) in ARF include volume overload, hyperkalemia, severe metabolic acidosis, uremic complications such as pericarditis and encephalopathy, or simply treatment of a rapidly rising BUN and serum creatinine. It is often better to start RRT preemptively to make room for the obligate volume intakes incumbent in providing nutritional, antimicrobial, and pressor support to the critically ill patient than to await volume overload. Although peritoneal dialysis is still used and is an acceptable treatment in certain circumstances, most patients with ARF receive either intermittent hemodialysis (IHD) or one of the forms of continuous renal replacement therapy (CRRT) discussed later in detail. (Chapter II-1c).

For IHD, short femoral vein catheters are the least optimal access because they are accompanied by high recirculation rates and reduced clearances. Internal jugular vein catheters are preferred because they spare subclavian vein cannulation, thus avoiding the complication of subclavian vein stenosis, which can preclude future successful upper extremity vascular access. However, in the critically ill patient access comes at a pre-

mium, and one often must take what is available.

The value of *early* initiation of dialysis in ARF or *intensive* dialysis in ARF merits discussion. Current practice is to initiate hemodialysis at BUN levels ≤ 100 mg/dL. This is based on a series of historically controlled retrospective studies, over 2 – 4 decades ago, which suggested but did not prove in a statistically significant manner that early initiation of hemodialysis is better. For instance, in one series of 500 patients [33], the overall mortality decreased from 42 – 27% when patients dialyzed prior to 1968, with an average BUN of 164 mg/dL at initiation of dialysis, were compared to those dialyzed after 1968, when the average BUN at initiation of dialysis was 93 mg/dL. Similarly it was reported that mortality decreased from 77 – 51% when dialysis was begun at a BUN of 150 mg/dL rather than 200 mg/dL in patients with ARF [20].

In a prospective evaluation of different intensities of dialysis in the treatment of ARF in Vietnam War casualties [12], patients paired based on similar injuries were maintained with predialysis serum creatinine levels of 5 mg/dL or 10 mg/dL, respectively. Statistically significant differences were not present in the 18 patients. However, the mortality rate observed was 36% in the more intensively dialyzed group versus 80% in the other patients. Subsequently [24], no advantage for intensive dialysis was detected in a group of 34 patients, paired by ARF etiology, initiated on dialysis when serum creatinine increased to > 7.5 mg/dL and dialyzed to maintain predialysis serum creatinine of either ≤ 5 mg/dL or between 9 – 11 mg/dL.

Limitations of these studies need to be emphasized in terms of design and application to the type of ARF population managed in intensive care unit settings today. Current data on the value of earlier initiation or more intensive dialysis in critically ill patients are urgently needed. This is highlighted by a recent retrospective analysis in 842 patients with dialysis-requiring ARF, in which, adjusting for the Cleveland Clinic Foundation ARF scoring system (an index of severity), survival correlated positively with delivered dialysis dose across a broad range of severity scores [48].

Using models developed from calculating total nitrogen appearance (generation) over a 5 day period in a group of patients receiving CRRT, it has been predicted that some 50% of hypercatabolic ARF patients would require at least 6 intermittent hemodialysis treatments per week to maintain a peak predialysis BUN < 100mg/dL [9]. Large patients (> 90 kg) would predictably fail to achieve this target even with daily dialysis. In contrast, any number of the available modifications of CRRT can easily provide for this intensity of dialysis.

Choices between CRRT and IHD are generally made based on the hemodynamic stability of the patients, volume control issues, and local availability of resources and trained staff. In general in intensive care unit (ICU) patients with ARF, there is a group whose prognosis is so bleak that differences in the relative efficacies of currently available treatment modalities within the group may be small. Likewise in ARF that is uncomplicated, nonoliguric, and secondary to a single insult in an otherwise healthy patient, the prognosis may be equally good regardless of the dialytic modality chosen. However, there is a large intermediate group for whom differential cost-effectiveness data relating to CRRT vs. IHD is clearly needed.

Increased dialysis membrane biocompatibility in intermittent hemodialysis has been associated with improved recovery of renal function and a trend toward increased patient survival [27]. A second prospective study also found a lower survival rate in patients dia-

lyzed with nonbiocompatible cuprophane membranes [55]. Finally, a retrospective, nonrandomized analysis implicated membrane biocompatibility in outcomes in ARF [43]. However, a third prospective study did not confirm a difference in either the rate of recovery of renal failure or patient survival based on membrane biocompatibility [34]. This was a smaller study, and there were possible confounding differences between the 2 dialysis membrane groups in terms of the proportions of patients with diagnoses of ischemic ATN and nephrotoxic ATN.

Accelerating Renal Recovery

Specific treatments targeted at renal regeneration and enhancing recovery from ARF remain to be established into clinical practice. Among the general interventions, it is clear that ongoing exposure to triggering factors may prolong the maintenance phase of ATN. Avoidance of nephrotoxic insults and maintenance of euvolemia and organ perfusion are critical. Avoidance of dialysis membranes with poor biocompatibility profiles and/or hypotension during dialysis treatments may be important.

Managing Complications of ARF

Infectious complications account for a large proportion of the mortality in dialysis-requiring ARF. The patients are immunocompromised (by uremia and other comorbid conditions), hospitalized and have numerous assaults on normal mucocutaneous barriers. Careful attention to aseptic care techniques, surveillance for infectious complications, and early and aggressive management form the best lines of defense.

Bleeding is also a common problem. Qualitative and quantitative defects in circulating procoagulants and platelets may complicate the uremic syndrome and predispose to bleeding. Stress and hematologic complications of multiple organ system dysfunction contribute. Strategies to control and treat bleeding are as for any critically ill patient with the following added observations: 1 – 2 doses of intravenous desmopressin (DDAVP) 0.3 μg/kg may enhance clotting through the release of endothelial cell stores of von Willebrand factor; conjugated estrogens (0.4 mg/kg daily) have a slower but sustained procoagulant effect; aggressive dialysis without heparin can partly ameliorate the anticoagulant action of uremic serum; maintaining a hematocrit > 30% enhances clotting ability; and cryoprecipitate may also promote clotting in the uremic patient.

ARF – Specific Syndromes

Hepatorenal syndrome refers to a type of functional ARF, in the setting of hepatobiliary disease, that is characterized by a relatively hyperosmolar urine and a urine sodium concentration < 10 mM. Hepatorenal syndrome is a diagnosis of exclusion. Specifically there is a requirement to outrule prerenal, renal and postrenal etiologies. It occurs most often secondary to alcohol-induced hepatic cirrhosis but occasionally complicates the course of fulminant acute viral hepatitis, biliary tract obstruction or surgery, hepatic malignancies, and partial hepatic resections. Severe hepatic failure with ascites, jaundice, and encephalopathy usually accompanies this syndrome. The prognosis of hepatorenal syndrome is poor, with a mortality of 80 – 95%.

Survival is generally dependent on effective liver regeneration or liver transplantation. When liver function is restored by liver regeneration, liver transplantation, or by renal transplantation into a recipient with normal liver function, RBF and GFR return to acceptable levels.

Patients with advanced liver disease have an impaired capacity to generate urea and also have reduced generation of creatinine as a consequence of asthenia. Thus, in patients with liver disease significant renal impairment may be present with only borderline elevations in BUN and creatinine. The classic pattern of hepatorenal syndrome is that of an acute oliguric form with rapid onset and progressive renal failure. It is unclear, however, whether renal function is initially normal in such classic presentations. A commonly seen clinical presentation is the patient with advanced liver disease whose renal failure progresses more slowly over weeks or months, but otherwise fits the description of hepatorenal syndrome.

Hepatorenal syndrome is characterized by avid tubular reabsorption of salt and a FE_{Na} < 1%; by an intact urinary concentrating ability and a urine osmolality that exceeds the serum osmolality; by a bland urine sediment without increased cells or formed elements, and with no more than 1+ proteinuria. Other causes of prerenal disease can produce the same clinical picture. Differentiating between these often rests on a careful volume challenge with colloid and saline. Sometimes central venous pressure monitoring will be required to prevent volume overloading the patient. If tense ascites is present, the simultaneous relief of this by large volume or total paracentesis while infusing colloid is sometimes useful. Prerenal azotemia will respond to such maneuvers with a rapid recovery of function, whereas hepatorenal syndrome typically responds less favorably.

Glomerular pathology was universally present in a prospective series of 18 consecutive recipients undergoing native kidney biopsies at the time of liver transplantation for end-stage liver disease [16]. Abnormalities included minor changes, glomerulosclerosis, membranoproliferative glomerulonephritis, and IgA nephropathy. The significance of cirrhosis-associated glomerular pathology is unknown, and it is rare for glomerular disease to be a dominant feature of renal failure syndromes in advanced liver disease. In hepatitis C-infected patients, the presence of glomerular proteinuria or red cell casts may be indicative of an underlying membranoproliferative glomerulonephritis (MPGN).

The finding of granular and tubular epithelial cell casts in urine microscopy is not uncommon in patients with renal failure and liver disease. By clinical definition, these patients do not have hepatorenal syndrome but rather evidence of structural tubular damage, indicating ATN. The etiology of ATN in this setting may be nephrotoxic or a continuum of prolonged renal hypoperfusion resulting in ischemic renal injury consequent on the same pathophysiologic processes that lead to the hepatorenal syndrome. Initially the FE_{Na} may be < 1% when ATN complicates liver failure but increases to levels > 1% with time.

Hepatorenal syndrome is a multifactorial process. Hemodynamic changes with widespread peripheral arterial vasodilation, increases in arteriovenous shunting, and increased vascular capacitance accompany hepatic failure. Activation of the sympathetic nervous system and renin-angiotensin system is well documented. Evidence has accumulated implicating alterations in vasoactive substances, including nitrous oxide, endothelin and vasodilator and vasoconstrictor prostaglandins, both systemic and intrarenal, in advanced liver disease. The result is intense renal arterial and arteriolar vasoconstriction

Table 5. Causes of Rhabdomyolysis

Traumatic
Direct muscle injury
Nontraumatic
Increased energy consumption
Postexertional muscle injury
Postseizure injury
Heat stroke
Reduced energy production
Hereditary enzyme deficiencies
Ischemia
Diabetic ketoacidosis
Hypokalemia
Hypophosphatemia
Miscellaneous
Inflammatory myopathies
Infectious myopathies
Drugs
Sepsis syndrome
Toxins

with decreased RBF and GFR and a state of functional renal failure.

Continued preferential accumulation of ascitic fluid can be understood as a sequela of splanchnic vasodilation, portal hypertension, and low plasma oncotic pressures shifting Starling's forces to promote localization of free fluid in the peritoneal space. Refractory ascites in selected patients may provide an indication for transjugular intrahepatic portosystemic shunts, peritoneovenous shunts, or liver transplantation. Unfortunately, neither of the first 2 options appears to prolong survival in patients with advanced liver disease and refractory ascites [53, 60]. Both can be associated with serious complications. The decision to aggressively manage the patient with hepatorenal syndrome (including the provision of renal replacement) hinges on whether liver regeneration or liver transplantation is anticipated for a given patient. Short of one or the other of these outcomes, renal replacement may only prolong the dying process.

When candidates with hepatorenal syndrome are transplanted, increased hospital morbidity and length of stay, but comparable patient survival at one year and acceptable actuarial patient survival at 5 years (60% vs. 68%, $P < 0.03$ for patients with and without hepatorenal syndrome, respectively) has been described [26]. Recovery of dialysis independence was usual, and the incidence of ESRD after liver transplantation in patients who had hepatorenal syndrome was 7%, compared with 2% in patients who did not have hepatorenal syndrome.

Pigment-related Nephrotoxicity

Rhabdomyolysis is a syndrome characterized by muscle fiber dissolution and release of intracellular contents into the extracellular space and circulation. The occurrence of myoglobinuric ARF is common. It has been studied since the classic descriptions of the "crush syndrome" complicating the London bombing raids during World War II [6]. Hemoglobin, likewise a heme pigment, is also capable of precipitating ARF.

Muscles make up approximately 40% of body tissue and contain large quantities of myoglobin. A classification of the causes of rhabdomyolysis is listed in Table 5. Muscle hyperthermia accompanying strenuous physical exertion, convulsions, septic rigors, or malignant hyperthermia may precipitate rhabdomyolysis. Ischemic injury below a major arterial occlusion; inflammatory disorders such as polymyositis, and various hereditary and infectious muscle disorders have also been implicated. Many medications may mediate muscle injury, including cyclosporine

and HMG-CoA inhibitors increasingly used in combination in transplant patients. Alcohol can be implicated in the generation of traumatic and nontraumatic rhabdomyolysis. The latter is often due to hypophosphatemia during calorie refeeding, and is preventable with careful monitoring and phosphate supplementation. Hypokalemia is also described as causative for rhabdomyolysis.

Among the many etiologies of hemolysis/hemoglobinemia, those most likely to contribute to ARF combine rapid and extensive hemolysis with situations in which decreased renal perfusion may simultaneously coexist, e.g. disseminated intravascular coagulation (DIC), incompatible blood transfusions, and infectious causes of hemolysis such as malarial or clostridial infections. Hemoglobinuria appears to result in ATN only when associated with other systemic abnormalities, especially dehydration, shock, and acidosis.

Cellular ATP depletion, intracellular calcium overload, and myocytolysis characterize the events at a muscle cell level in rhabdomyolysis. Severe local capillary leakiness can lead to rapid widespread third spacing of fluid in the muscular interstitial spaces. The pathomechanisms of heme pigment-related ATN are shared by myoglobin and hemoglobin. Both pigments are filtered at the glomerulus, although hemoglobin much less freely than myoglobin because of its larger size (molecular weight 68 vs. 17 KD) and because of the presence of a hemoglobin-binding protein, haptoglobin, in the plasma. Intrarenal vasoconstriction is common as a consequence of uncorrected volume depletion due to third spacing of fluid. This vasoconstriction leads early on to a low FE_{Na} and a concentrated and acidic urine. In turn, this favors the precipitation of heme pigments and Tamm-Horsfall protein in the distal nephron with consequent intratubular obstruction. Delayed urine transit and reduced GFR prolong the exposure of proximal tubular cells to heme pigments and maximize pigment uptake by endocytotic absorption in the proximal tubule. Proximal tubular heme loading leads to cell injury by complex mechanisms in which ischemia, ATP depletion, and oxidant stress induced by intracellular release of catalytic iron molecules are all thought to play a role [63].

Because myoglobin is so much more freely filterable, the urine but not the plasma is pigmented in myoglobin-associated ATN, while both urine and plasma are pigmented in hemoglobinuric states. Heme-positive urine and the absence of red blood cells on sediment microscopy are characteristic findings. A definitive diagnosis can be made by demonstrating myoglobin or hemoglobin directly in the urine by counterimmunoelectrophoresis. In rhabdomyolysis, the diverse nature of the intracellular contents released into the circulation is reflected by marked elevations in plasma levels of creatine phosphokinase, phosphate, uric acid, potassium, and creatinine. The elevation in creatinine is more rapid than in other types of ARF, reflecting both muscle release and reduced plasma clearance. Thus, the BUN:creatinine ratio is typically < 10. Severe hyperkalemia may be seen. The release of intracellular potassium and phosphorous can obscure the pathogenic role that low levels of these electrolytes may play in the etiology of the condition. Symptomatic hypocalcemia due to high phosphorous levels and deposition in muscle beds is common. In the recovery phase of myoglobinuric ARF, hypercalcemia may be seen as a consequence, in part, of calcium mobilization from skeletal muscle.

The prevention of rhabdomyolytic-induced ATN rests on early and aggressive volume replacement, enhancing the rapid clearance of heme pigments, and providing protection to proximal tubular cells. Retrospective analyses provide overwhelming support for aggressive

volume replacement. When urine output allows, it has been recommended that after resuscitation at least a 12 L mannitol-alkaline diuresis be provided in the first 24 hours [2]. To provide for this, large volumes of fluid may be required early on to replace the third-spaced volume loss. Alkalinization is recommended to produce a urine pH > 6.5. This prophylactic measure aims to reduce Tamm-Horsfall-heme pigment precipitation, which occurs more readily in an acid urine – although it may simply exert its protective effect through a saline diuresis. Mannitol probably exerts its protective beneficial effect as a proximal tubular diuretic rather than the theoretical suggestions that it has a beneficial vasodilatory effect or hydroxyl radical scavenging effect. The emphasis is on maintaining a volume-replete state and a solute diuresis with an alkaline urine. If mannitol is used, monitoring is mandatory to avoid an excessively hyperosmolar state. The amount of bicarbonate required to produce an alkaline urine varies widely. We prefer to administer the bicarbonate as part of an isotonic solution (0.45% saline solution with 75 mmol $NaHCO_3$), because bolus doses of hypertonic bicarbonate predispose to hypernatremia. Once renal failure is established, these interventions are of no benefit, and the principles of management are the same as for any form of ATN. Avoidance of volume overload then becomes mandatory, and it should be remembered that pigment-induced ARF may often be accompanied by severe hyperkalemia, hyperphosphatemia, and hypocalcemia, which can necessitate early dialysis.

Radiocontrast Procedures and ARF

ARF after radiocontrast-related procedures is a common problem in the inpatient setting.

The importance of ARF after radiocontrast procedures in an in-patient hospital population was recently emphasized in a well-controlled retrospective cohort analytic study [36]. In this analysis, the development of renal failure after a radiocontrast procedure was strongly and independently correlated to mortality risk in a multivariate analytic model developed and validated for the cohort being studied. Over 16,248 patients were screened to identify 183 index subjects who developed ARF (1.1% of those undergoing radiocontrast-related investigations). The overall mortality rate was 34% vs. 7% in those who did or did not develop ARF, respectively. The study did not firmly establish contrast nephropathy as the underlying etiology of ARF in all the observed cases. However, the results do pertain to an at-risk inpatient population undergoing contrast procedures and, as such, are important.

Atheroembolic disease complicating angiographic procedures is discussed elsewhere. This next section focuses on the outcome and clinical significance of classic cases of contrast nephropathy. The classic presentation of contrast nephropathy is that of deteriorating renal function occurring within 1 – 2 days, peaking within 3 – 5 days, and resolving within 7 – 10 days of radiocontrast exposure. Most cases are nonoliguric and do not require dialysis. The urine sediment early in contrast nephropathy may be bland, and urinary indices suggest prerenal injury (low FE_{Na}). Later, tubular epithelial cells and granular and tubular epithelial cell casts are seen, indicating tubular injury. The mechanisms of contrast nephropathy are thought to involve a reduction in RBF, an imbalance between tubular workload and oxygen supply, and a direct tubular toxicity of the contrast agent.

Contrast nephropathy occurs in only approximately 3% of patients without identifiable risk factors in most large prospective

population studies. With appropriate controls, the true incidence of ARF in low-risk patients (nonazotemic, nondiabetic) is even less: 2.1% and 1.3% in those exposed and not exposed, respectively, to contrast media [14]. Preexisting chronic renal impairment, diabetes, and multiple myeloma are the comorbid risk factors most often cited as predisposing to contrast nephropathy. Whether preexisting renal insufficiency truly increases the incidence of contrast nephropathy or simply increases the sensitivity of detecting renal injury as a result of the exponential relationship between creatinine and GFR is debatable. It is clear, however, that contrast nephropathy is more of a problem in those with impaired baseline kidney function. For example, the implications of a 10 mL/min decrease in GFR are different for the patient with a baseline GFR of 20 mL/min, compared to a patient with a baseline GFR of 120 mL/min. The incidence of contrast nephropathy appears directly proportional to the degree of chronic renal insufficiency. Moore et al. report an incidence of 4.7%, 14.3%, and 20%, respectively, for those with baseline creatinine levels in the ranges of 1.5 – 1.9, 2.0 – 2.4, and 2.5 – 2.9 mg/dL, respectively [44].

Table 6. Toxins, Drugs and Acute Tubular Necrosis

Radiocontrast
Heme pigments
Immunoglobulin light chains
Platinum/Mercury/Chromium/Uranium/Bismuth/Silver
Organic solvents
Aminoglycosides
Amphotericin B
Penicillins/Cephalosporins/Imipenum
Vancomycin
Ifosfamide
Interleukin-2
Cyclosporine/FK506
Intravenous immune globulin
Streptozotocin
Mannitol

Having diabetes and chronic renal insufficiency seems to further predispose to more clinically serious contrast nephropathy. Risk is again proportional to baseline GFR, and of those with severe chronic renal impairment 50 – 90% may develop contrast nephropathy. For some, the ARF will be irreversible. In contrast to azotemic diabetics, diabetics with normal renal function are not at a significantly increased risk for contrast nephropathy, according to recent studies. Likewise, multiple myeloma in the absence of other predisposing risk factors (e.g. volume depletion, renal insufficiency) does not absolutely mitigate against contrast exposure [42]. It is wise, however, to be careful with all diabetics and patients with multiple myeloma, regardless of baseline serum creatinine levels. Any prerenal state, whether or not functionally significant prerenal azotemia has been documented, should be considered an at-risk state for contrast-induced renal injury. To better appreciate the procedural risk, it is prudent to recommend a recent serum creatinine precontrast exposure for all inpatients and for outpatients who are elderly, diabetic, hypertensive, or predisposed to decreased renal perfusion.

Prophylaxis of contrast nephropathy is important. Indications for contrast-related procedures need to be clearly defined, especially for high-risk patients. Measures should be taken to correct predisposing factors such as volume depletion. Optimal prophylaxis includes avoidance of concomitant nephrotoxic exposures and ensuring a euvolemic state. Maintaining a saline hydration, with 0.45% saline solution, 1 mL/kg body weight/hr, commenced 12 hours before and maintained for 12 hours after contrast exposure is indicated for at-risk patients. In a randomized,

prospective study, saline alone provided better protection against acute contrast-induced decreases in renal function than saline combined with either mannitol or furosemide [58]. The prophylactic usefulness of other agents in high-risk patients remains uncertain. However, the volume of contrast to which the high-risk patient is exposed should be minimized [40]. Likewise, low-osmolality contrast media has been shown in a large, prospective, randomized trial to reduce the incidence of contrast nephropathy in azotemic patients with and without diabetes [54].

Drug-related ARF

See table 6 for summary.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs can lead to decrements in GFR and elevations in BUN and serum creatinine when used in clinical circumstances characterized by prostanoid-dependent RBF. The pathomechanism is clearly hemodynamic. NSAIDs do not exert this effect in euvolemic individuals with normal renal function because in this state, maintenance of RBF and GFR is independent of prostaglandins.

A decline in absolute or relative effective arterial blood volume results in compensatory humoral mechanisms to maintain blood pressure. As in most hormonal systems, these vasoconstrictor hormones participate in a negative feedback loop by promoting the renal production of vasodilatory substances, primarily prostaglandins. Intrarenal prostaglandins work both to modulate vasoconstriction by lessening preglomerular vascular tone, thus preserving GFR, and to preserve medullary oxygen hemostasis by preferentially increasing medullary regional perfusion. NSAIDs inhibit the cyclooxygenase (COX) I and II isoenzymes that metabolize arachidonic acid substrate in a rate-limiting step in prostaglandin synthesis. In states of diminished effective arterial blood volume, they inhibit the protective effects of prostanoid on RBF. The consequence is ARF with rising BUN and creatinine levels, sodium and water retention, and frequent hyperkalemia. Onset is typically within 24 hours of taking a dose. The effect occurs with all commonly used anti-inflammatory drugs at therapeutically prescribed doses. Low-dose aspirin for platelet inhibition does not produce the effect. Sulindac is an NSAID which the kidney can rapidly metabolize and inactivate. However, acute hemodynamic renal failure has also been described with this drug. In addition to leading to ARF, NSAIDs produce other nephrotoxic effects including an allergic interstitial nephritis (of slow onset) and nephrotic syndrome secondary to minimal change disease (MCD) or membranous glomerulonephritis. In the future, selective Cox II inhibitors will be available and may mediate anti-inflammatory effects at doses that minimally alter intrarenal hemodynamics [23].

Angiotensin-converting Enzyme (ACE) Inhibitors

In discussing drug-induced hemodynamic ARF, it is necessary to comment on ACE inhibitors and angiotensin II (Ang II) receptor blockers. These 2 classes of drugs are associated with predictable declines in GFR in patients with chronic renal insufficiency or humoral-dependent RBF, especially in patients

with bilateral renal artery stenosis. In these circumstances autoregulatory mechanisms protect GFR by preferential Ang II-mediated postglomerular arteriolar constriction. Loss of this increased efferent arteriolar tone follows introduction of any of the drugs belonging to these 2 classes of agents. The decline in GFR is generally acceptable as a hemodynamic and reversible consequence. Indeed, it is desirable in order to slow subsequent progressive declines in GFR in macroproteinuric renal diseases and diabetes. However, severe baseline renal failure and hyperkalemia are limiting factors to the use of these agents. Very rarely, ARF may result from ACE-associated renal infarction. This occurs in patients with severe baseline renovascular disease in whom abrupt hypotensive effects of drug administration drop the perfusion pressure across a tight renal artery stenosis and precipitate complete renovascular occlusion. Although rare, this occurrence dictates caution in using these agents in patients with suspected severe renal artery stenosis.

Antibiotics

Aminoglycosides have a major role in the treatment of gram-negative microbial infections. They are small molecules (approximately 500 KD), negatively charged, minimally protein-bound in plasma, and excreted unchanged in the urine. Their plasma clearance roughly equals GFR. After filtration in the kidney, reuptake of a small percentage of aminoglycosides in the proximal tubule is mediated via the process of adsorptive pinocytosis. Once intracellular, the pinocytosed vesicle fuses with lysosomes and localizes the aminoglycosides to this organelle. The intracellular half-life of an aminoglycoside is up to 4 – 5 days in the renal cortex vs. a plasma half-life that is measured in hours. Accumulation of high concentrations of the drug occurs in proximal tubular cells.

The nephrotoxicity that complicates some 10 – 20% of courses of aminoglycoside antibiotics is the result of this accumulation. The aminoglycosides interfere with lysosomal phospholipids leading to a so-called "phospholipidosis" characterized in part by intracellular accumulation of myeloid bodies that contain aggregates of undigested phospholipid membranes damaged by the aminoglycosides. Other drugs may cause phospholipidosis without causing renal failure. At what point and through what additional mechanisms aminoglycosides mediate their nephrotoxicity needs further clarification.

The consequences of aminoglycoside toxicity are proximal tubular cell injury with enzymuria and the shedding of microvilli and cells into the tubular lumen. Intraluminal obstruction and transtubular back leak are important pathophysiologic mechanisms. Serum creatinine and BUN levels characteristically rise 7 – 10 days into a course of aminoglycoside treatment. In uncomplicated cases where aminoglycosides represent the sole insult to the kidneys, cessation of the antibiotic typically is followed by a course of nonoliguric ARF, not requiring dialysis intervention, with a gradual recovery of renal function over a couple of weeks. However, a more common situation is the additional contribution of aminoglycosides to renal failure in combination with other renal insults, including ischemia, contrast agent and sepsis. The relative contribution of aminoglycosides in this setting is more difficult to establish.

While the therapeutic indications for aminoglycosides have been clearly established over time, the avoidance of nephrotoxicity remains a challenge. Advanced age, preexisting renal disease, liver disease, long or repeated courses of antibiotic, volume depletion and/or a prerenal state, hypokalemia, hypo-

magnesemia, and concurrent exposure to additional nephrotoxic agents predispose to aminoglycoside nephrotoxicity. Avoidance of some of these predisposing factors, such as volume depletion, is possible. Consideration may be given to shorter courses when antibiotic sensitivities are available to guide treatment.

Dosimetry pertaining to aminoglycosides is another area of active research. The bactericidal effect of aminoglycosides correlates with the peak blood level achieved, while the nephrotoxic side effect correlates with trough blood levels. As 100% of the drugs are renally cleared, preexisting or developing renal failure during a course of aminoglycosides will lead to increasing plasma trough levels unless the dosage interval is appropriately lengthened to allow for clearance. The widespread use of measuring serum concentrations of aminoglycosides has been disappointing in terms of its impact on the incidence of nephrotoxicity. This is not to say that measurement of levels and avoidance of high trough levels should be ignored, but rather emphasizes that nephrotoxicity may occur even when levels are maintained in the appropriate range.

Daily dosing of aminoglycosides in patients with normal renal function was introduced a number of years ago to exploit several known properties of this class of drugs, namely that bactericidal effect correlates with peak drug levels, that a post-antibiotic effect is present suppressing bacterial growth at levels below the minimal inhibitory concentration (MIC), that the length of the post-antibiotic effect increases with higher peak levels of the drug, and that adsorptive pinocytosis in the proximal tubule is a saturable process. It was hoped that once-daily dosing would enhance or sustain efficacy while reducing the incidence of nephrotoxicity. Recommendations have been published for high-dose, extended-interval aminoglycoside regimens including dose adjustment guidelines for those with creatinine clearances in the range of 20 mL/min to normal [46, 50]. At present there is moderate to strong evidence of probable clinical benefit for daily dosing in gram-negative infections; moderate evidence of a limited benefit or no difference in gram-positive infections; little or no evidence for benefit in pediatric, geriatric, pregnant, obese, burn, or cystic fibrosis patients, or in those with creatinine clearances < 20 mL/min; and indications that high-dose extended interval regimens may be inappropriate for enterococcal infections [22]. The application of computer-generated alert systems may also have a role in reducing the incidence or severity of drug-related nephrotoxicity [52].

Amphotericin B Nephrotoxicity

Amphotericin B, a polyene antibiotic, presently remains the most effective agent for the treatment of deep-seated and disseminated fungal infections. Amphotericin B interacts with lipid sterols present in the outer membranes of susceptible microorganisms. Fungi contain ergosterol as part of their membranes, hence their sensitivity to polyenes such as amphotericin B. In contrast, bacteria do not have lipid sterols in their membranes and are resistant to the effects of this class of drug.

The renal toxicity of amphotericin B is characterized by distal renal tubular acidosis (RTA), hypokalemia, an ADH-resistant urinary concentration defect, reduced GFR, and occasional symptomatic hypomagnesemia and salt wasting. The integration of amphotericin B with cell membranes in the distal nephron leads to formation of pores of sufficient size to allow abnormal solute trafficking. The distal RTA is believed to be secondary to an increased passive permeability of the luminal membrane and back diffusion of hydrogen

ion, rather than an active transport failure. Likewise, potassium wasting, which may be profound, occurs in the context of increased membrane permeability in the distal nephron and passive flux along a favorable electrochemical gradient. Increased aldosterone-dependent potassium-sodium exchange is not involved. Although the hypokalemia may aggravate or cause a nephrogenic diabetes insipidus, membrane effects increasing the permeability of the medullary collecting ducts to urea may partly efface the medullary hypertonicity gradient and account for some of the failure to elaborate a concentrated urine. Hypomagnesemia occurring as a result of amphotericin B toxicity may contribute to exaggerated hypokalemia that is resistant to aggressive correction until the magnesium has first been replaced.

In contrast, acute rises in serum potassium levels have been described following the rapid infusion of amphotericin B in anephric patients [15]. This may occur because of leakage of potassium from the intracellular compartment unopposed by exaggerated urinary losses. The patient with established renal failure receiving amphotericin B needs to be carefully monitored for this complication.

Pathologic mechanisms by which amphotericin B precipitates ARF include both a renal vascular effect producing ischemia and direct tubular toxicity. Greater levels of toxin in the kidney caused by longer courses of treatment and/or larger doses overwhelm the ability of the cell to repair membrane defects. The renal toxicity is clearly dose dependent. While GFR can return to normal after discontinuation of the drug, a fraction of patients have irreversible damage. Chronic renal failure was observed in 44% of patients receiving a total dose of > 4 g and in 17% of patients receiving < 4 g total dose [5].

Preventive strategies include salt loading and avoidance of concomitant volume depletion and additional nephrotoxic insults. Protective roles for alkalinization, aminophylline administration and calcium channel blockers remain unproved. A small prospective study showed no beneficial effect of mannitol, while a case control study reported a 12.5 fold greater risk of nephrotoxicity with prophylactic use of furosemide. The place of liposomal and other lipid-based formulations of amphotericin B requires continued investigation. An advantage proposed for these formulations is a reduction in nephrotoxicity based on characteristics that favor selective drug delivery to the reticuloendothelial system, macrophages, and sites of infection. These formulations also decrease the systemic side effects that often accompany the infusion of free amphotericin B.

Miscellaneous Antibiotics

Other antibiotics implicated in the generation of ATN include the beta-lactam group of antibiotics, i.e. penicillins, cephalosporins, and imipenum. Except for cephaloridine, nephrotoxicity is a rare side effect of these drugs. The mechanism of injury may be via lipid peroxidation in the case of cephaloridine, or mitochondrial injury in the case of the other antibiotics. Selectivity for the proximal tubule is a result of dependence on the organic amino acid transport system. The administration of imipenum with cilastin serves to reduce its toxicity, because cilastin inhibits enzymatic cleavage of imipenum by brush border dehyropeptidases in the proximal tubule. The nephrotoxicity of current vancomycin preparations is much less than before, and synergistic nephrotoxicity between these preparations and aminoglycosides has not been convincingly demonstrated. Tetracyclines may worsen azotemia via an antianabolic effect leading to an elevation in BUN, but not

serum creatinine, in patients with preexisting azotemia. Accumulating levels of tetracycline may also produce a toxic tubular cell injury in patients with liver disease. Acute allergic interstitial nephritis complicating antibiotic usage is not discussed here.

Antineoplastic Drugs and Heavy Metals

A variety of heavy metals have been shown to produce ARF with proximal tubular cell necrosis. Salts of mercury, arsenic, chromium, uranium, bismuth, silver, and platinum are potent nephrotoxins. Exposure is usually occupational with the exception of the platinum salts, which are used therapeutically.

Cisplatin, which describes the organic compound cisdiaminodichloroplatinum, is a chemotherapeutic agent. Its nephrotoxic effect is dose limiting. Interventions that decrease nephrotoxicity are potentially beneficial in terms of facilitating larger doses and greater efficacy. After a single dose of cisplatin, mild reductions in GFR may be seen in up to 25% of patients. Repeated doses may give rise to nephrotoxicity in up to 75% of patients. While the acute effects are generally reversible, permanent irreversible damage may follow repeated exposure. The reduction in GFR is generally delayed 1 – 2 weeks after dosage. The mechanism is understood to depend on uptake and slow transformation of cisplatin in proximal tubular cells. Aquation of the cis chloride sites of cisplatin in the relatively "low chloride" intracellular environment is thought to produce toxic-charged species. The typical histologic features are injury in the tubulointerstitial compartment. Particularly susceptible are the S_3 segments of the proximal tubule, and less so the distal tubule and collecting duct.

Enzymuria, rarely measured in clinical practice, may be the earliest indication of tubular injury. Following on this, urinalysis findings of tubular proteinuria and granular and tubular epithelial cell casts are seen. Hypomagnesemia complicates 50% of cases. Urinary magnesium wasting may contribute to secondary hypokalemia and hypocalcemia. This defect typically resolves within a few weeks of the last cisplatin dose, but has been observed to persist for several years.

Prevention of cisplatin nephrotoxicity is approached by employing an aggressive saline diuresis and also by avoidance of concurrent exposure to other nephrotoxic drugs, such as aminoglycosides. In general, a euvolemic state is required, after which a bolus dose of saline of approximately 500 mL and infusion of as much as 150 – 250 mL per hour thereafter is initiated before, continued throughout, and for 4 – 6 hours after cisplatin has been infused. Normal saline or hypotonic half-normal saline has been used with or without mannitol. It has been observed that larger doses of cisplatin remain nephrotoxic despite these measures, but can be tolerated when administered in hypertonic (3%) saline solutions. This raises the possibility that optimal protection requires not just hydration with increased urine flow and reduced contact between tubular cells and the drug, but an additional chloriuresis and hyperchloremic state. Continued investigation of other agents that might reduce nephrotoxicity is worthwhile. With careful application of a prophylactic hydration protocol, renal toxicity is no longer per se a treatment limiting complication of cisplatin chemotherapy. Other chemotherapeutic platinum analogues have been developed, including carboplatin and ormaplatin. Renal dysfunction has been described with both, and hydration is important when using these drugs.

Other Antineoplastic Drugs

The alkylating agent *ifosfamide*, unlike its parent compound cyclophosphamide, is associated with nephrotoxicity. It also shares with cyclophosphamide the property of urotoxicity. Mesna, a synthetic sulfhydryl compound, protects against the urotoxicity of the acrolein and chloroacetalalahyde metabolites of ifosfamide, but it does not protect against the renal parenchymal insult [57]. Ifosfamide nephrotoxicity is characterized by proximal tubule cell injury and Fanconi's syndrome with proximal RTA, phosphaturia, glycosuria, uricosuria and aminoaciduria. Aggressive supplementation of electrolytes may be necessary, and in children a propensity to hypophosphatemic rickets has been described. While GFR is generally only mildly reduced, severe ARF may also occur. Preexisting chronic renal insufficiency or prior cisplatin exposure may be a predisposing factor to ifosfamide-induced renal injury. General preventive measures are advisable. Experimental data has suggested glycine, via a membrane protective effect, is worth investigating as an agent with potential clinical applications.

Recombinant *interleukin-2* is employed as an immunomodulatory agent in various drug protocols for patients with metastatic adenocarcinoma. A lymphokine normally produced by activated T-cells, it is sometimes given in combination with lymphokine-activated killer cells. A predictable septic shock-like syndrome often follows its administration, with decreased systemic vascular resistance, increased cardiac output, capillary leakiness, and a transient requirement for crystalloid, colloid, and/or pressors to maintain perfusion pressure. Weight gains of 10 – 15% of body weight are not unusual. The renal lesion most commonly seen is a prerenal functional azotemia with characteristic urinary indices and rapid reversibility with restoration of RBF. Ischemic ATN may complicate its use. Rare cases of allergic interstitial nephritis and even RPGN have been described.

Nitrosureas associated with renal toxicity include streptozotocin, semustine, and lomustine. Of these, streptozotocin is the most likely to manifest acute toxicity. Fanconi's syndrome, mild reductions in GFR, and severe acute "nephrotoxic" ATN have all been described.

Mitomycin-C is notorious for the propensity for recipients to develop HUS as a delayed and dose-related complication of this drug. HUS is considered elsewhere in this text.

The drug *mithramycin-C* used occasionally to treat hypercalcemia of malignancy is associated with ARF when used as an antineoplastic agent. ARF, however, is rare when single doses are used to treat hypercalcemia, although it has been reported.

Gallium nitrate, another agent used to treat hypercalcemia of malignancy, may lead to ARF as a result of intratubular precipitation of calcium-gallium-phosphate salts. This was a major side-effect of short infusions of this drug in initial studies. Continuous infusions (200 mg/m^2 for 5 days) have been administered without severe nephrotoxicity.

A similar mechanism of intrarenal obstructive ARF is described with large doses of *methotrexate*. Intraluminal precipitation of the metabolite 7-hydroxy-methotrexate and methotrexate is favored by a concentrated acidic urine. Preventive strategies employing hydration, alkalinization, and folinic acid (to prevent systemic toxicity) generally work well. Low-dose chronic use of methotrexate is generally well tolerated. However, renal impairment can lead to significant drug accumulation and systemic toxicity.

Mannitol

Mannitol is the polyol of the sugar mannose. Administered intravenously, it is inert, remains in the extracellular compartment, and is freely filtered by the kidney. It is used clinically for its osmotic properties to reduce intracranial pressure and intraocular pressure, and occasionally for its diuretic properties. It has been used as prophylaxis for nephrotoxic ATN, although an incremental benefit of mannitol over and above that gained from solute diuresis is unproved. When mannitol infusion exceeds its rate of clearance, the drug accumulates in the extracellular space. The osmotic effects are exaggerated beyond the therapeutic targets of lessening intracerebral pressure to include excessive cellular dehydration and altered mental status, extracellular volume expansion with congestive heart failure (CHF) and pulmonary edema, and metabolic abnormalities such as hyponatremia, hyperkalemia, and metabolic acidosis. Less recognized is the potential for mannitol to paradoxically precipitate ARF [18].

Observations have connected hemodynamic effects of mannitol at high and low doses with worsening medullary hypoxemia. Therefore, injury is most likely secondary to ischemia. A dose of 0.25 mg/kg every 4 hours used to lower intracranial pressure appears to be therapeutically effective, and higher doses have been shown to portend a poor prognosis. The osmotic gradient between the extracellular and intracellular compartment attributable to mannitol determines the fluid shift. It is recommended that during mannitol use, the osmolal gap rather than the serum osmolality be monitored. This is because a serum osmolality of 310 mOsm/kg in the setting of a sodium of 140 mM indicates a very different mannitol concentration in the extracellular fluid than the same serum osmolality in the setting of a sodium of 120 mM. ARF has been observed with peak osmolal gaps of 74 ± 39, and 107 ± 17 mEq/kg. The osmolal gap should be prevented from reaching these high levels by decreasing or holding mannitol doses while following renal function closely. ARF-complicating mannitol infusion reverses rapidly when the drug is discontinued.

Immunosuppressive Drugs

Nephrotoxic effects of immunosuppressive drugs are discussed in detail elsewhere in this text. Briefly, both cyclosporine and tacrolimus (FK506), commonly used immunosuppressants, can contribute to acute elevations in BUN and serum creatinine in a number of ways. First, both produce dose-dependent intrarenal preglomerular vasoconstriction with a reduction in glomerular hydrostatic pressure and GFR. This effect occurs within the therapeutic dose range used for transplantation. Second, nephrotoxic effects on both microvasculature and tubules are described. Early posttransplantation endothelial injury can initiate a thrombotic microangiopathic syndrome with ARF. This is fortunately uncommon. Acute tubular toxicity early post-transplant is also a dose-related adverse effect. Both cyclosporine and FK506 produce a chronic arteriolopathy and chronic toxicity with irreversible kidney damage that is discussed in detail elsewhere (Chapter III-4).

ARF in Bone Marrow Transplantation

Up to 40 – 50% of patients receiving a bone marrow transplant may develop some degree of ARF. Often dialysis is required, and the mortality rate is as high as 80 – 90%. A variety of etiologic factors, singly or in combination, may play a role. Included are volume deple-

tion; exposure to nephrotoxic antineoplastic, antibiotic, or immunosuppressive drugs; and an acute uric acid nephropathy complicating cytoreduction therapy. Additional etiologies include a syndrome of functional renal failure, hepatorenal syndrome-like in its presentation, that accompanies veno-occlusive disease of the liver. It is primarily a hemodynamic renal failure that occurs coincident with veno-occlusive disease during the first 2 – 3 weeks after transplantation. The outcome of the ARF is dependent on the outcome of the veno-occlusive disease. In the past, myohemoglobinuric ARF was seen to complicate marrow transplantation. This was usually the result of red cell lysis and hyperthermia complicating the use of dimethyl-sulfoxide as a cryoprotectant. Autologous and allogenic marrow is now red cell depleted, and patient management is specifically designed to avoid volume depletion. As a result, pigment nephropathy is now rare. Tumor infiltration is a recognized but exceedingly rare cause of ARF. For instance, although autopsy studies report a prevalence of 63 – 90% renal infiltration in chronic lymphocytic leukemia (CLL), reports of impaired renal function are uncommon.

Tumor Lysis Syndrome

Tumor lysis syndrome is characterized by ARF complicating the release of large quantities of intracellular molecules by necrotic tumor cells. It occurs most often in non-Hodgkin's lymphoma and acute lymphocytic leukemia (ALL). These are tumors with large bulk and very rapid growth phases. The syndrome can occur without treatment as tumors outgrow their blood supply, or it may complicate glucocorticoid or cytoreductive therapies. Characteristic metabolic abnormalities are hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute, typically oliguric renal failure. Volume depletion often plays a predisposing role. Renal failure is due to intraluminal precipitation of crystals of uric acid and, to a lesser extent, calcium phosphate. This occurs in the distal nephron leading to intraluminal obstruction. Precipitates and sludging are also seen in the medullary microvasculature.

Hydration, high-dose allopurinol, and alkalinization attenuate the occurrence and severity of this syndrome. Prevention is not absolute. Alkalinization to reduce uric acid precipitation should be titrated to achieve a urine pH of 7.0. If the urine pH rises above 7.0, alkali should be held because an alkaline urine favors calcium phosphate precipitation. Due to the scale of release of potassium and phosphorous from intracellular stores, early and intensive dialysis is frequently needed to prevent life-threatening hyperkalemia and extensive metastatic calcification. Early dialytic support can be life saving. Renal function typically recovers well in patients who survive.

Future Directions

A recent publication resulting from an NIH consensus conference, organized to discuss future directions for research in ARF, included recommendations for establishment of a multicenter database to be developed to facilitate outcomes research in ARF; an emphasis on prospectively validating risk stratification measures in ARF to be employed in the design of new randomized clinical trials; new clinical trials in ARF to investigate the roles of low-dose dopamine, hemodynamic monitoring, nutritional supplementation, di-

alysis modalities, dialysis delivery/intensity, and new adjunctive agents developing out of basic science research; and enhanced support of basic research addressing the cellular and molecular basis of renal tubular injury, changes in cell differentiation, cell repair, cell death, and organ recovery [19]. These various goals address urgent needs of physicians, patients, and families when approaching difficult decisions in the management of patients with ARF.

Exciting new treatments need to be investigated. Experimental data are accumulating to suggest exogenous administration of epidermal growth factor (EGF), hepatocyte growth factor (HGF), or insulin-like growth factor-I (IGF-1) might be beneficial in ARF syndromes [35]. Effects of growth factors are likely to be directly exerted on tubular cells. IGF-1 is also anabolic and modulates blood flow to increase RBF and GFR. In a double-blind, placebo controlled, prospective, randomized study of patients undergoing suprarenal aortic or renal artery surgery, the administration of IGF-l was found to be feasible and associated with a smaller postoperative decline in renal function [21]. However, no cases of established ARF were documented in the study, and the use of IGF-l did not significantly impinge on the outcomes or hospital course. IGF-l has also been safely administered to patients with chronic renal failure, where it augments RBF and GFR. The therapeutic value of arginine-lysine-aspartate (RGD) peptides is also worth investigating [25]. These peptides bind up B1 integrins on tubular cells, thus preventing the cells from binding to each other. They may also ameliorate aggregation of intraluminal debris and cells, thus preventing luminal obstruction in ATN. Antibodies against the cell adhesion molecule ICAM-l or against other inflammatory mediators may reduce the inflammatory component of the ischemic-reperfusion injury in the maintenance phase of ATN [31]. Enhanced blood flow to hypoxic tubules with newer vasoactive agents, such as those modulating endothelin-mediated vasoconstriction, may also have value in human ARF.

Advances in supportive therapies for dialysis-requiring ARF must focus on clarifying the respective roles of continuous and intermittent treatment modalities. Since outcomes in ESRD are inversely related to the dialysis dose delivered, intensive dialysis needs to be pursued with further evaluation of its role in ARF. It will be necessary to modify quantification techniques of the delivered dialysis dose in ARF to account for the confounding factors posed by the non-steady state metabolic characteristics, variable volumes of solute distribution, and impaired tissue perfusion that exist in this population of patients. Prescriptions may need to be related to urea generation as a marker of catabolic rate, and delivered dose may require dialysate-side quantification of solute clearance [9].

Improvements in dialysis and hemofiltration, however, only replace the filtrate function of the kidneys. Renal tubules also have important reabsorptive, homeostatic, metabolic, and endocrine functions. Replacement of these lost functions through cell therapy or tissue engineering in patients with ATN could be helpful in providing more complete support during the maintenance phase of ATN, and might enhance a speedier recovery and improve overall prognosis. Cell therapy is an evolving strategy that uses cells as vehicles for delivery of drugs by taking advantage of their synthetic and metabolic properties. A “bioartificial” renal-tubule device that uses epithelial progenitor cells is currently being tested in preclinical trials [29]. Its potential additive benefits in treating syndromes of ARF are also worthy of continued investigation, as it provides a unique and novel supportive strategy.

Conclusion

ARF is a serious, common, complicated and costly medical illness. Other comorbid conditions may accompany ARF, often as a presentation of multiple organ dysfunction. Management of these issues is outside the scope of this chapter. The precise contribution of ARF to these other serious comorbid conditions is sometimes difficult to determine. The dictum that people *die with* and not *of* ARF, however, suggests that if only we could manage all the other combined problems better, our current sophistication in terms of renal replacement therapy is good enough to ensure survival. However, it has been suggested that renal failure per se affects mortality rates [36] and that improving biocompatibility of dialysis treatments enhances survival [27]. It is thus more likely that the high mortality rate in ARF is determined by complicated interdependent relationships among all the existing comorbid conditions, including ARF itself.

Much progress needs to be made in both the prevention and treatment of patients with ARF. We believe that interventions which improve the treatment of ARF or shorten its duration will translate into lives saved.

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