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Disorders of Urine Volume in the Critically Ill Child

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This article will provide a pathophysiologic basis for the assessment of critically ill children who have developed disorders of urine volume. The anatomical and pathophysiologic causes of oliguria and polyuria are considered. The physiologic basis for the use of urinary sodium and osmolarity as a guide to the assessment of patients with disorders of urine volume are discussed in detail. In addition, guidelines for the management of children with acute renal failure, with particular emphasis on the consideration for nutritional support of these patients, is discussed as a part of the comprehensive approach to this problem. This article emphasizes an understanding of the pathophysiology of salt and water excretion by the kidney as a foundation to the diagnosis and management of patients with oliguria and polyuria.

In a critically ill patient, the volume or rate of urine excretion is used, frequently, as an index of cardiovascular stability, cardiac output, and peripheral perfusion. In fact, in some instances, the adequacy of parenteral fluid therapy is assessed and adjusted according to urine output. Such assumptions concerning urine output and judgments about fluid therapy are not only an oversimplification of complex renal physiology, but also hazardous for patient management. Under homeostatic conditions, 20-25 percent of cardiac output is distributed to the kidneys, 500 cc/minute in an adult. Approximately 20 percent of this volume is filtered by the glomerulus (100 cc/minute) and, over 24 hours, the proximal tubule is presented 144 liters of glomerular filtrate (i.e., potential urine) and 20,160 mEq (460 g) of sodium. The tubules and collecting ducts reabsorb 98-99 percent of this filtrate (i.e., 142 liters of fluid and 456 g of sodium) which results in a final urine output of 2 liters/day which contains 4 g of sodium. In most circumstances, the kidney will react to maintain intravascular volume and plasma tonicity by balancing the processes of filtration, reabsorption, and excretion. For example, by autoregulation of resistance in the afferent and efferent arteriole, glomerular filtration rate (GFR) can be maintained through a wide range of blood pressures and renal perfusion [1]. Moreover, the intact kidney responds to a variety of stimuli in a reasonably predictable and reproducible manner so that an assessment of urinary electrolytes can be helpful in evaluating patients with oliguria or polyuria.

However, pathophysiologic alterations in the production or reabsorption of tubular fluid render urine output a poor index of renal function. If GFR is maintained but the reabsorptive processes are enhanced by a reduction in intravascular volume, as in simple dehydration, or diminished renal perfusion, as occurs in congestive heart failure, a patient may be relatively oliguric while renal function is quite normal. Alternatively, GFR may be severely reduced but a concomitant reduction in the volume of tubular fluid which is reabsorbed will result in a normal or increased

urinary volume. In fact, in the extreme example of non-oliguric acute renal failure (ARF), the amount of urine excreted may equal the entire volume of glomerular filtrate produced. Thus, it becomes apparent that the oliguric patient may have relatively normal renal function and the polyuric patient could have acute or chronic renal failure. Assessment of renal function in children and adolescents must be based, therefore, on absolute values or changes in the blood levels of urea nitrogen (BUN) and creatinine (Cr) and/or the clearance of creatinine or inulin [2,3].

In a stable, euvolemic state, a child or adolescent with normal renal function and intact kidneys will generally excrete 1.5–3 cc/kg/hour of urine. This estimate is derived from the volume of urine expected in a pediatric patient receiving parenteral fluids at a maintenance rate of infusion. Maintenance fluid therapy is designed to maintain water and electrolyte homeostasis with minimal renal compensation [4]. The volume of fluid needed for maintenance therapy is composed of two parts: *(1)* evaporative (insensible) losses and *(2)* urinary losses. Evaporative or insensible water requirement is approximately one-third of total maintenance requirement and consists of electrolyte-free water. During maintenance fluid therapy, urinary losses are expected to have an osmolarity of 300 mOsm/L and a specific gravity of 1.010. Caution must be taken that the patient can achieve an isotonic urine and, under homeostatic conditions, urinary losses account for two-thirds of total maintenance fluid requirement. Estimates of total maintenance requirement can be made from the following table:

1–10 kg	100 cc/kg/day
11–20 kg	1,000 cc + 50 cc/kg > 10/day
21–80 kg	1,500 cc + 20 cc/kg > 20/day

This sliding scale approach is based on the concept that water and electrolytes are lost in direct proportion to the kilocalories expended. If 120 ml of water is required for every 100 Kcal metabolized and if water of oxidation is 17 ml/100 Kcal and preformed water is 3 ml/100 Kcal, it becomes apparent that, in this system, 100 ml of water are needed for each 100 Kcal expended. Thus, the calculations from the sliding scale provided an estimate of caloric expenditures, maintenance fluid requirements, and expected urine volume under homeostatic conditions.

ASSESSMENT OF OLIGURIA

Based on the expected urine volume, a child or adolescent excreting less than 0.8 cc/kg/hour of urine should be assessed for oliguria. Classically, the causes of oliguria have been divided into pre-renal, renal, and post-renal categories. However, such a classification is neither physiologically based nor accurate. Accordingly, the classification shown in Table 1 forms the basis of our approach to this problem.

Anatomic Causes First consideration should be given to the obstruction or occlusion of the major anatomical components of the renal system: artery, vein, ureter, and bladder. It must be emphasized that oliguria will not result from the occlusion of the artery, vein, or ureter to only one kidney, unless the contralateral kidney is absent or non-functional. Thus, one must suspect bilateral renal artery, vein, or ureteral obstruction if these sites are to be implicated as the cause of oliguria. Renal artery thrombosis is rare in children although occasionally encountered in newborn infants as a complication of umbilical artery catheterization. The usual clinical presentation for this problem is acute hypertension in a young infant.

TABLE 1
Causes of Oligo-Anuria
(<0.8 cc/kg/hour urine)

A. Obstruction or occlusion of major anatomical sites:
   1. Both renal arteries
   2. Both renal veins
   3. Both ureters
   4. Bladder outlet

B. Pathophysiologic response to:
   1. Decreased intravascular volume or impaired renal perfusion
   2. Fixed or established renal insult—acute renal failure
   3. Non-physiologic anti-diuretic hormone secretion

Likewise, renal vein thrombosis occurs almost exclusively in newborn infants. This diagnosis should be suspected when a patient develops an enlarging flank mass associated with the onset of hematuria, proteinuria, thrombocytopenia, and intravascular coagulopathy. The diagnosis of renal vein thrombosis may be difficult to establish and may require arteriography for confirmation. Bilateral ureteral obstruction should be considered in all children who develop oliguria because this is a potentially acutely correctable situation. Because partial ureteral obstruction produces polyuria and because most children with hydronephrosis present with an abdominal mass or urinary tract infection, ureteral obstruction is an uncommon cause of oliguria. Nonetheless, this possibility should be evaluated using non-invasive imaging techniques such as renal ultrasound [5,6]. The demonstration of two kidneys and the lack of a dilated renal pelvis in, at least, one kidney will essentially eliminate this diagnosis as the cause of oliguria. Several prospective studies have shown renal ultrasound to be reliable in assessing acute ureteral obstruction in adults [5,6]. Unless this diagnosis is highly suspected because of the clinical situation, potentially more risky or invasive procedures such as intravenous or retrograde pyelogram should not be done routinely. Lastly, bladder outlet obstruction must be evaluated in all children with oliguria, particularly male infants. In this condition, the bladder can be palpated quite often in children, especially boys with posterior urethral valves. Even if the bladder cannot be palpated, a catheter should be inserted into the bladder to rule out this potentially correctable cause of oliguria. If the patient has a bladder catheter it should be irrigated. Each of these anatomic sites should be considered prior to evaluation of the physiologic causes of oliguria.

Pathophysiologic Causes There are three pathophysiologic conditions in which oliguria occurs: *(1)* decreased intravascular volume or impaired renal perfusion, *(2)* acute renal failure, and *(3)* non-physiologic anti-diuretic hormone secretion. The renal response in each of these clinical settings is highly reproducible and well defined. Although each of these conditions will cause a fall in urine volume below expected levels, the urinary constituents, especially sodium and osmolarity, are characteristic and can be used diagnostically when the kidney has not been manipulated pharmacologically with vasodilators or diuretics (Table 2).

Decreased Intravascular Volume or Impaired Renal Perfusion

A decrease in intravascular volume results in a decrease in cardiac output and renal hypoperfusion. Thus, the renal response to either decreased intravascular volume or a primary fall in renal perfusion is similar. In this situation, the renal

TABLE 2
Urinary Sodium and Osmolarity in Evaluation of Oligo-Anuria

	Decreased Intravascular Volume or Diminished Renal Perfusion	Established Acute Renal Failure	Non-Physiologic ADH Secretion
Urinary Na mEq/L	<10	>50	>50
Fractional Na Excretion (FE_{Na})	<1%	>2%	>2%
Urinary osmolarity mOsm/L	>500	~300	>500
$\frac{\text{Urine}}{\text{Plasma}}$ osmolarity	>1.5	0.8–1.2	>2.0
BUN/serum creatinine	>20	Progressive increase in both	<20

$$\text{Fractional Sodium Excretion} = \frac{\text{Urine}}{\text{Plasma}}\ \text{Na} + \frac{\text{Urine}}{\text{Plasma}}\ \text{Creatinine}$$

tubules remain intact and a marked increase in the reabsorption of solutes and water occurs throughout the nephron. An increase in filtration fraction (GFR/renal plasma flow) produces an increase in peritubular oncotic pressure and results in enhanced reabsorption of tubular fluid in proximal tubular segments. The decrease in renal perfusion stimulates the secretion of renin by the juxtaglomerular apparatus, and thereby aldosterone production is increased and produces sodium reabsorption from the distal tubule. Release of anti-diuretic hormone in response to decreased intravascular volume increases water reabsorption in the collecting duct. Thus, the urinary sodium concentration is quite low (< 10 mEq/L) and the urinary osmolarity is high (> 500 mOsm/L). In premature infants and children less than one year of age, urinary sodium < 20 mEq/L and osmolarity < 400 mOsm/L would be expected values [7]. If the patient is hyponatremic (serum sodium 130 mEq/L), then fractional sodium excretion (FE_{Na}) is a more accurate index of renal sodium handling. Fractional sodium excretion is the amount of sodium excreted ($U_{Na} \times V$) expressed as a ratio of the amount of sodium filtered (GFR $\times$ P_{Na}). If one substitutes creatinine clearance ($U_{Cr} \times V/P_{Cr}$) for GFR, the FE_{Na} can be expressed as $U/P_{Na} \div U/P_{Cr}$. Similarly, urine-to-plasma ratio of osmolarity is a better reflection of water reabsorption in the hyponatremic patient. For example, if a patient had a serum sodium of 120 mEq/L, the estimated plasma osmolarity would be 240 mOsm/L, and a urine osmolarity of 360 mOsm/L would be a urine/plasma osmolar ratio of 1.5 and would represent significant water reabsorption. The increased solute reabsorption which occurs in this condition pertains to constituents other than just sodium, such as urea. Normally, 30 percent of filtered urea is reabsorbed, and an increased proportion is reabsorbed when renal perfusion falls. Since creatinine is not reabsorbed by the tubule, the enhanced urea reabsorption results in a BUN-to-creatinine ratio > 20, which is often referred to as "pre-renal" azotemia, but is actually due to the pathophysiologic response of the kidney to diminished perfusion. Renal perfusion may be reduced to the extent of impairing GFR, at which time serum creatinine will rise. In contrast to patients with an established acute renal failure where the serum creatinine increases by 0.5–1.5 mg/dl each day, patients

with impaired renal perfusion tend to have a slower rise in serum creatinine such that the values tend to remain at the same level for several days at a time and to increase in a stepwise fashion rather than a linear pattern.

Clinical conditions which are associated with decreased intravascular volume include dehydration secondary to vomiting, diarrhea, nasogastric drainage, or third space losses. Repletion of intravascular volume with appropriate fluid therapy in this clinical setting will result in increased urine output. Occasionally, children with nephrotic syndrome will become oliguric while edematous because of decreased intravascular volume secondary to reduced plasma oncotic pressure. Remission of the nephrotic syndrome or the infusion of albumin to restore intravascular volume will alleviate the oliguria in these children. Patients with congestive heart failure have a primary decrease in renal perfusion because of diminished cardiac output despite adequate or expanded intravascular volume. In this situation, therapy should be aimed toward improved cardiac function rather than repletion of intravascular volume. Similarly, children with acute glomerulonephritis [8,9,10,11,12,13] or hemolytic uremic syndrome [14,15,16,17,18] have increased intravascular volume but diminished renal perfusion which occurs at a level of the glomerular capillary loop. In patients with acute glomerulonephritis, the increase in renal vascular resistance is caused by the intense inflammatory reaction in the glomeruli and in patients with hemolytic uremic syndrome micro-thrombi occlude the glomerular capillaries. The oliguria associated with these conditions resolves only as the renal disease improves and heals. In both of these "renal" causes, the tubules remain intact and the renal response in terms of urinary sodium concentration and osmolarity is physiologically identical to the "pre-renal" causes such as dehydration and congestive heart failure. Thus, the use of the term "pre-renal" to describe the renal pathophysiologic response to decreased intravascular volume or diminished renal perfusion is inaccurate and confusing. Lastly, patients with the hepato-renal syndrome will have oliguria and urinary sodium concentrations which are low and urinary osmolarity which is high. In fact, it would appear that this syndrome is a vasomotor phenomena rather than an intrinsic renal lesion. The correction of the oliguria in these patients occurs only when the liver failure improves, which is rare.

Acute Renal Failure (ARF)

The renal response to a fixed or established acute renal insult is complex [19,20,21,22]. Although the specific mechanisms involved may vary according to the type and intensity of the acute renal injury, an acute loss of GFR and paralysis of tubular function are the characteristic features of acute renal failure (ARF). An increase in renal vascular resistance [23,24] combined with back-leak of tubular fluid [25,26,27,28,29] and intratubular obstruction [30,31,32,33] result in a nearly complete cessation of GFR. Clinically, this is reflected in an increase in both BUN and serum creatinine on a daily basis. It is important to remember that although GFR is virtually non-existent early in ARF, the absolute value of serum creatinine will not reflect the profound loss of GFR because this value increases only 0.5–1.5 mg/dl/day. Thus, in patients with ARF, the rate of change in serum creatinine, rather than the actual value itself, is the best index of the level of GFR, and a progressive increase in BUN and creatinine is a characteristic feature of this syndrome. Changes in BUN will be affected by a variety of factors such as catabolic rate, protein load, and medications, including steroids and antibiotics. Consequently, the rate of change in BUN is not a specific index of the level of GFR. The second feature which is characteristic of ARF is diminished tubular function. Ironically, the term

"acute tubular necrosis" is a better description of tubular function than anatomic morphology in ARF [34]. Thus, the small volume of urine which these patients produce has a high sodium concentration (> 50 mEq/L) and elevated FE_{Na} (> 2 percent). Since both the concentration and dilution of tubular fluid require intact tubular function, these patients have urine which is isotonic to plasma (i.e., urinary osmolarity of 280–300 mOsm/L and urine-to-plasma osmolar ratio of 0.8–1.0). In ARF, a dilute urine would be as unexpected as a concentrated urine and an isotonic urine is the most consistent feature of this syndrome. In fact, a low urinary sodium concentration and FE_{Na} have been reported in some patients with ARF induced by contrast media.

The clinical conditions which are associated with the development of ARF include hypotension/shock, renal ischemia, nephrotoxins, drugs, hyperuricemia, asphyxia, and sepsis [35,36,37,38,20,39]. Most often, more than one potential causative agent can be identified, but in some circumstances, ARF will develop without a clearly defined renal insult. In this regard, several factors should be remembered: *(a)* dehydration or volume depletion will increase the susceptibility to develop ARF from a minor insult [40,41]; *(b)* hypoxia combined with acidosis will produce a more profound loss of renal function than either factor alone; *(c)* nephrotoxins, especially aminoglycoside antibiotics, usually produce a non-oliguric ARF initially with oliguria developing later in the course of the renal injury [42,43,40,44], and some drugs may potentiate the relative nephrotoxicity of other agents [45]; and *(d)* sepsis may produce ARF from endotoxins without concomitant hypotension [46].

Studies in both experimental animals [47,48,49,50,51] and man [52,53,54] have indicated that the fall in GFR can be attenuated significantly or even eliminated by administration of saline, mannitol, furosemide, or other agents prior to the renal insult. Interestingly, the common denominator among all of these perturbations which will protect against the development of ARF is the initiation of a solute diuresis prior to the renal injury [51,55,56]. Thus, in those clinical situations where an acute renal insult is anticipated, such as renal vascular surgery, open heart surgery using cardiopulmonary by-pass, or administration of large volumes of contrast media, the patient should be well hydrated with isotonic fluid and/or a natriuretic agent should be given prior to the renal insult.

At the present time, the treatment of ARF consists of supportive care until the kidney recovers from the acute insult. In this regard, several potential problems must be anticipated and managed: *(1)* fluid therapy, *(2)* electrolyte problems, *(3)* acidosis, *(4)* hypertension, *(5)* dialysis, and *(6)* nutrition. For the child with oliguric ARF, fluid therapy should be designed to replace extra-renal fluid losses. In large part, this means providing adequate fluids to account for evaporative (insensible) fluid requirements plus losses from other sources such as nasogastric drainage, chest-tube drainage, or urine output, if any. Evaporative or insensible losses are composed of solute-free water which is lost through the skin and lungs. This water is utilized for thermal regulation and to humidify the inspired air. Under ordinary conditions, these losses are approximately 30–35 percent of total maintenance volume [4]. Sweat is not included in evaporative fluid losses. Because insensible losses are evaporative, the ambient humidity and temperature will have profound effects on the magnitude of these losses. Patients receiving humidified air via a nasotracheal tube or dwelling in a mist tent will have a considerable reduction in insensible losses, which must be taken into account in calculating maintenance needs. Similarly, patients with hyperthermia or tachypnea or under a radiant warmer will have exag-

gerated evaporative losses. Under ordinary circumstances, 33 percent of evaporative losses occur through the lungs and 66 percent from the skin, while total evaporative losses are one-third of maintenance requirements. The volume of fluid calculated to replace evaporative losses should be given as an electrolyte-free solution. Fluids lost from other sources should be replaced in amounts equal to those being excreted with a solution similar in composition to that being lost only if the patient is not edematous, volume overloaded, hypertensive, or in congestive heart failure. The adequacy of fluid therapy in patients with ARF is judged best by changes in body weight and serum sodium concentration. If an appropriate volume and composition of fluid have been administered, the weight of the patient should decrease by 0.5–1 percent per day because of caloric requirement, and the serum sodium should remain stable between 130–140 mEq/L. A more rapid loss of weight or increase in serum sodium would suggest that inadequate fluids had been given, while a gain in weight combined with a fall in serum sodium would imply overhydration. If hydration has been inadequate, one should assess those factors which would increase insensible fluid losses such as hyperthermia, increased activity (particularly seizures), tachypnea, or a dry ambient environment such as that produced by radiant warmers. If excessive fluids have been given, one should re-evaluate insensible fluid requirement in terms of factors which would reduce evaporative fluid losses, such as humidified air from a respirator, hypothermia, sedation, or reduced activity.

Two major electrolyte problems are encountered commonly in patients with ARF. Hyponatremia (serum sodium $<$ 130 mEq/L) may be present at the time the diagnosis of ARF is made or may occur during the course of therapy. When present at the onset of ARF, hyponatremia is usually the result of overzealous administration of fluids in an attempt to increase urine output prior to the recognition of oliguric ARF. When a fall in serum sodium occurs during the management of a child with ARF, it is usually because of an overestimate of evaporative fluid requirement. In both cases, hyponatremia has occurred because of excessive administration of fluids and not the excretion of sodium. If the hyponatremia is profound (serum sodium $<$ 120 mEq/L) and the patient has central nervous system manifestations such as obtundation or seizures, a rapid correction of the hyponatremia would be indicated and the serum sodium can be increased by 10 mEq/L with the infusion of hypertonic (3 percent) saline. This solution contains 450 mEq/L of sodium, and 12 ml/kg will increase serum sodium by 10 mEq/L. It must be emphasized that *(1)* the administration of sodium is not usually required to correct the hyponatremia associated with ARF, *(2)* fluid restriction is the primary and essential mode of therapy, and *(3)* the infusion of sodium may be hazardous for the patient and lead to volume expansion, hypertension, and congestive heart failure.

Because the kidney is the primary source for potassium excretion and because the extra-renal mechanisms which are required for potassium adaptation occur slowly over several weeks, hyperkalemia is frequently encountered in patients with ARF [57]. Often the insult which causes the ARF produces significant systemic tissue damage with the release of intracellular potassium from necrotic cells or in response to acidosis. Since potassium ions move out of cells as hydrogen ions move into cells, serum potassium levels are not a direct index of total body potassium and must be interpreted with respect to acid-base status. For example, a serum potassium of 6 mEq/L is less ominous in a patient with a mild metabolic acidosis (pH 7.30; bicarbonate, 15 mEq/L) than in a patient with a metabolic alkalosis (pH 7.50; bicarbonate, 35 mEq/L). Despite the same level of serum potassium, the patient with

alkalemia would be expected to have a larger total body burden of potassium. Largely because of its cardiac toxicity, hyperkalemia represents a life-threatening complication of ARF and must be treated promptly and aggressively. If mild electrocardiographic changes such as peaked T-waves are present, the administration of sodium bicarbonate (1–2 mEq/kg over 10–30 minutes) or Kayexalate (1 g/kg/dose) by mouth or enema may be effective in reducing serum potassium levels. Kayexalate is a sodium polysterene-sulfonate resin which exchanges sodium for potassium. It has the advantage of net potassium removal, with the disadvantage of sodium delivery and fecal impaction if not excreted. If significant electrocardiographic changes such as widened QRS complex or arrhythmia are present, the infusion of 10 percent calcium gluconate solution (0.5–1 ml/kg) over 5–10 minutes with electrocardiographic monitoring or the administration of an insulin (0.2 units/kg/hour) and glucose solution (1 g/kg/hour) should be started. Although these solutions will lower the serum potassium level acutely and prevent a fatal cardiac arrhythmia, their effectiveness is transient because they do not result in net potassium removal. Consequently, these modalities are used until other therapies such as dialysis can be started. Finally, either hemo or peritoneal dialysis should be instituted if hyperkalemia is severe (serum potassium > 8 mEq/L) or intractable.

A mild metabolic acidosis associated with an increased anion gap is an inevitable consequence of reduced renal function because of the retention of hydrogen ions, sulfate, and phosphate. Ordinarily, this mild acidosis can be easily compensated by respiratory mechanisms and does not require specific intervention. If the acidosis is contributing to the development of hyperkalemia or respiratory compensation is impaired, sodium bicarbonate can be administered. Generally half the estimated deficit (20 − serum bicarbonate) is replaced: ½ deficit × weight in kg × 0.5 = mEq Na HCO_3 to be given. When sodium bicarbonate is infused, three points of caution should be remembered: *(a)* standard bicarbonate preparations contain approximately 1 mEq HCO_3 per ml, are, therefore, hypertonic solutions, and must be given slowly to avoid marked changes in plasma tonicity and central nervous system complications, *(b)* bicarbonate is an effective buffer only if the CO_2 produced from the reaction H + HCO_3 is removed by adequate ventilation. Thus, in situations in which ventilation is impaired, the infusion of bicarbonate will have little net buffering effect until ventilation is adequate. In those clinical settings in which a severe acidosis persists because of poor tissue perfusion or a lactic acidosis develops, dialysis may be necessary to correct the acidosis, *(c)* patients with ARF frequently have hyperphosphatemia with mild hypocalcemia, and rapid correction of acidosis with the development of alkalemia can induce tetany or seizures.

Hypertension is frequently encountered in children with acute renal failure. While judicious administration of fluids will lessen the degree and frequency of hypertension in children with ARF, a substantial proportion of patients will require treatment to avoid developing hypertensive encephalopathy. The management of hypertensive crisis or accelerated hypertension requires special consideration in children [58]. Heart failure, papilledema, and/or encephalopathy mandate prompt and intensive antihypertensive treatment. Hypertensive encephalopathy in children may be manifested as headache, irritability, or convulsions. These symptoms appear to be related more to the rapidity of the rise in blood pressure than to a specific level of pressure. Papilledema and retinal hemorrhages and exudates are less commonly seen in children with acute symptomatic hypertension than in adults [59]. Children with acute elevations in blood pressure may convulse and yet not manifest

papilledema or significant funduscopic changes. Diazoxide, a non-diuretic sulfonamide derivative, is the drug of choice for the treatment of acute or accelerated hypertension in children [60]. It should be administered rapidly (in less than 30 seconds) in an intravenous dose of 5 mg/kg/dose (maximum, 300 mg per dose). The onset of action is rapid and the effect on blood pressure dramatic. The patient rarely becomes hypotensive, and the effect may last several hours to a day, during which time additional medications, such as hydralazine, can be added to obtain long-term control of blood pressure. Repeated administration of diazoxide may be associated with sodium retention, and prolonged use should, therefore, be combined with a natriuretic drug, such as furosemide; frequently, a combination of a diuretic, such as furosemide, and diazoxide are used from the onset.

Parenterally administered hydralazine (0.2 mg/kg/dose, intramuscularly or intravenously) is also an effective and potent antihypertensive agent [58]. Its onset of action is one to two hours, and its duration of action is four to eight hours. Unfortunately, nausea, vomiting, and headache commonly occur in children treated with parenteral hydralazine, and these side effects may confuse the clinical picture when hypertensive encephalopathy is present. In situations in which intravascular volume overload is the prominent factor and renal function is relatively well preserved, such as acute glomerulonephritis [61], intravenous administration of furosemide (2 to 10 mg/kg/dose) may prompt a brisk diuresis and concomitant lowering of the blood pressure. Sodium nitroprusside is a potent and effective parenterally administered antihypertensive [62]. This drug must be dissolved in 5 percent dextrose solution and given as a continuous infusion with the dose and rate of infusion titrated against the arterial blood pressure. A dose of 1 μg/kg/minute is usually effective in producing a prompt fall in pressure. In patients with renal insufficiency, the blood levels of a metabolic product, thiocyanate, must be carefully monitored. The drug should be discontinued if the thiocyanate levels reach or exceed 10 mg/dl; this metabolic product can be removed by dialysis.

In those patients with symptomatic severe hypertension (i.e., hypertensive crisis), treatment should be initiated with diazoxide, given intravenously. A response should be seen in 5 to 15 minutes; if there has been no effect in 30 to 60 minutes, the dose should be increased by 25 to 50 percent to a maximum dose of 300 mg, and repeated. Concomitantly, furosemide is usually administered intravenously, unless the patient is anephric or has been anuric for a prolonged period. If these measures are ineffective and the patient remains symptomatic, treatment with sodium nitroprusside should be instituted. In asymptomatic children with severe hypertension but without overt hypertensive crisis, treatment can be initiated with parenterally administered hydralazine. The dose of this medication can be increased by 50 to 100 percent every one to two hours (to a maximum dose of 15 mg) until the desired effect has been achieved. Once the blood pressure has been controlled acutely, a long-term therapeutic regimen must be instituted.

The indications for the initiation of dialysis in patients with ARF remain controversial. Although several investigators have suggested that dialysis should be started "early" and the BUN maintained below 100 mg/dl, there is no clear evidence to support this approach as the routine management of all patients with ARF. It is generally agreed that certain complications of ARF would be absolute indications for dialysis: *(1)* severe or persistent hyperkalemia; *(2)* intractable hypertension, congestive heart failure, or pulmonary edema from volume overload; *(3)* severe and persistent acidosis; and *(4)* neuromuscular instability or uremia. In most cases,

however, dialysis should be initiated prior to the onset of one of these complications of ARF. The decision to start dialysis therapy in a patient with ARF should depend on an assessment of the clinical setting for each patient and an anticipation of the period of ARF based on the type and severity of renal insult which has occurred. This treatment modality should not be initiated because of artificial criteria such as the level of BUN, number of days of oliguria, level of serum creatinine, and so on. In large part, such decisions require an understanding of the potential benefit and risk of dialysis as well as an appreciation of the natural history of ARF in various clinical situations and should not be based on arbitrary criteria which may not reflect the level of renal function or degree of uremia. With the development of refined techniques for enteral and parenteral nutrition, dialysis has become an important adjunct for the support of nutritional requirements of patients with ARF. Although hemodialysis is technically feasible even in neonates [63], peritoneal dialysis is frequently more practical because it alleviates the need for vascular access. Both modalities of dialysis are comparably effective in the management of patients with ARF and the choice of a specific technique will depend on *(1)* size of the patient, *(2)* availability of vascular access, *(3)* integrity of the peritoneal membrane and abdominal cavity, and *(4)* local experience and expertise.

Nutritional support for the patient with ARF must be given serious attention. The insult which causes the ARF frequently renders the patient severely catabolic. Recent data would suggest that healing and repair of the kidney, as well as other organs, require the provision of adequate calories and energy metabolism [64,65,66]. Because of volume restriction secondary to oliguria, the supply of metabolic substrate is severely limited in patients with ARF. In this regard, it is important to remember that a 5 percent glucose solution given at a maintenance rate over twenty-four hours provides only 20 percent of basic calorie needs, i.e., "protein-sparing" calories. Thus, when the rate of infusion is reduced, as occurs in oliguric ARF, the proportion of caloric expenditures provided falls dramatically unless the caloric content of the infusate is increased. In 1967, Lee et al. [67] treated 45 adult patients with intravenous casein hydrolysates and lipid emulsion for 6 to 31 days during an episode of ARF. These investigators observed diminished weight loss and more prompt recovery in this group of patients. Subsequently, several investigators [68,69,70] demonstrated that the intravenous infusion of essential amino acids and glucose would result in positive nitrogen balance, better healing of wounds, maintenance of weight, amelioration of uremic symptoms, and diminished levels of blood urea nitrogen in post-operative adult patients with ARF. In 1973, Abel and associates [71] provided controlled evidence of the efficacy of the administration of essential amino acids with hypertonic glucose in ARF. These investigations compared the outcome of 28 patients treated with amino acids and hypertonic glucose to 25 patients given an isocaloric, isovolemic glucose infusion. Patients with congestive heart failure, endocarditis, hepatic failure, sepsis, persistent hypertension, or urinary obstruction were excluded from the study. In addition, the two groups were randomized for factors which might alter the course of ARF such as age, levels of BUN or creatinine prior to treatment, oliguria, and the interval from injury to intravenous therapy. In this relatively homogenous group of patients, the infusion of amino acid with hypertonic glucose had a dramatic effect on recovery from the episode of ARF. During the period of acute renal shutdown, the mortality rate was reduced from 56 percent in the glucose-treated patients to 25 percent in the patients receiving amino acids and glucose. Among the patients who required dialysis only 18

percent of those given glucose lived, whereas 65 percent of those treated with the amino acid-glucose mixture survived. In patients given amino acids, the serum creatinine concentration peaked on day two of therapy while this value continued to rise for seven days after initiation of treatment with glucose alone. Utilizing a slightly different amino acid mixture, in a larger group of 129 patients, Baek and associates [72] also noted an impressive decline in mortality from 70 percent in glucose-treated patients to 46 percent in patients given amino acids during an episode of post-operative ARF. In 1975, Leonard and co-workers [73] reported improved nitrogen balance but no effect on survival or duration of renal insufficiency in a small group of 20 patients with ARF treated with amino acids and glucose or glucose alone. Unfortunately, this was a heterogenous group of both medical and surgical patients, and the treatment groups were not randomized for factors which might alter the outcome. In fact, the amino acid-glucose-treated patients were older, had more pre-existing disease, and were more catabolic prior to initiation of therapy. Similarly, Abel et al. [74] failed to demonstrate increased survival with amino acid therapy for patients with acute renal failure complicated by congestive heart failure, hepatic failure, sepsis, or persistent hypertension. Unfortunately, there was no glucose-treated control group with similar complications. Thus, the results of administration of amino acids to patients with ARF is mixed. One possible explanation would be that the potential effect of this therapy in the more severely ill patients is obscured because of their heightened catabolic state and the limited ability to supply calories and nutrients which can be utilized for renal repair and regeneration. Because of limited clinical experience and conflicting reports concerning the efficacy of this modality, definitive indications for initiation of amino acid therapy in ARF cannot be established. The potential beneficial effect of increased caloric and nutrient content must be evaluated in the context of a given patient's clinical setting, local expertise in the performance of parenteral alimentation in children and adolescents, and the risks of this procedure, which include catheter placement injuries, sepsis, hyperglycemia, and electrolyte abnormalities [72,73].

It should be remembered that children may be able to take enteral nutrition during an episode of ARF. In such circumstances, the diet should be modified to account for the ARF, but the caloric intake should be maximized to offset the catabolic state associated with ARF. In large part, this will consist of restricting protein intake to 0.5–1 g/kg/day, limiting sodium to 2 g/day, and reducing potassium to 1.5 g/day. Although fluid intake will be restricted, free access to carbohydrates and fats should be encouraged. Once dialysis is initiated, the dietary and fluid restriction can be liberalized, or if continuous peritoneal dialysis is used, the diet can be relatively unrestricted. Thus, clinical judgments concerning nutritional needs and dialysis therapy must be made together and individualized, based on a specific clinical setting and needs of the patient.

Some patients will develop ARF without oliguria [42,44]. In the clinical setting of non-oliguric ARF, the urine constituents are the same as those in oliguric patients, but the etiology is more often related to nephrotoxic antibiotics, particularly the aminoglycoside category [43]. Experimental data would suggest that non-oliguric ARF develops when cortical perfusion is better preserved relative to total renal blood flow [40]. Although it has been proposed that potent diuretics can convert an oliguric ARF to a polyuric ARF, such therapy does not seem warranted for several reasons: *(a)* the use of furosemide and ethycrinic acid in high doses in patients with ARF is associated with significant and sometimes permanent hearing loss [75,76],

(b) conversion from oliguric to polyuric ARF does not result in more rapid return of GFR [75,76], and *(c)* the eventual prognosis is unchanged [75,76]. In patients with non-oliguric ARF, careful replacement of urine losses must be incorporated into the fluid management regime to avoid electrolyte disturbances.

The prognosis for patients with an established acute renal insult is dependent largely on the cause of ARF. With the availability of acute hemo and peritoneal dialysis for the replacement of kidney function, it is apparent that patients die with, not because of, ARF. Thus, the magnitude and severity of the total body insult become the limiting factors for most patients with ARF [77,78]. Recovery from oliguric ARF is heralded by an increase in urine output which occurs, on average, 10 to 14 days after the acute injury. In some situations the period of oliguria may be only two to three days, whereas some patients have ARF for 30 days or more. It is relatively difficult to predict the onset of recovery and, for patients with prolonged oliguria, the potential for recovery of renal function is even more difficult to assess. Once urine output reappears, there is usually an increase in volume for several days as GFR returns faster than tubular function and a significant diuresis may ensue. The BUN and serum creatinine does not usually fall until the diuresis has been established for several days. However, data from experimental animals [26] and man [27] would suggest that a significant amount of solute and water leaks back across the injured tubular epithelium during the early phase of recovery from ARF. Thus, the back leak of tubular fluid containing urea and creatinine across the tubule into the blood would result in the BUN and serum creatinine being an underestimate of GFR during the early period of recovery from ARF. The recovery of renal function is dependent on reperfusion of the previously vasconstricted kidney [47,79,80,24]. Thus, care must be taken to assure the maintenance of intravascular volume, cardiac output, and renal perfusion to promote recovery from ARF. In this regard, the diuresis which occurs during this phase of ARF should be replaced unless the patient has clear clinical signs of volume overload or edema formation. Moreover, drugs or procedures which may result in diminished renal perfusion should be avoided if possible. Most patients have a full recovery of renal function, although maximal concentrating ability may be impaired for several years [77,81,78].

Non-Physiologic Anti-Diuretic Hormone Secretion

Oliguria may be a mode of presentation for critically ill children with non-physiologic (inappropriate) anti-diuretic hormone (ADH) secretion because of the low renal solute load in these patients. Although this pathophysiologic process is frequently thought to be complex and clinically confusing, it is based on a relatively simple concept: the persistent excretion of a concentrated urine in the absence of physiologic stimuli for ADH release. If conceptualized from this perspective, the clinical findings in this syndrome are easy to understand, and the term non-physiologic ADH secretion is a clearer description of the syndrome than the more conventional term "syndrome of inappropriate ADH secretion" (SIADH). The secretion of ADH by the posterior lobe of the pituitary gland is closely regulated, under homeostatic conditions, by osmolar and volume receptors. A 2 percent increase in plasma osmolarity will result in the release of enough ADH to produce anti-diuresis [82], while a 1.2 percent decrease in plasma osmolarity will suppress ADH secretion sufficiently to produce a diuresis [83]. Baroreceptors, located in the carotid sinus [84] and left atrium [85] modulate ADH release in response to changes in intravascular volume. Although these physiologic monitors usually act in the

same direction, there is evidence that regulation of volume takes precedence over osmolarity when the two parameters conflict. Patients with non-physiologic ADH secretion have a persistently concentrated urine even though intravascular volume is normal or increased and plasma osmolarity is normal or decreased. Continual release of ADH results in increased water reabsorption from the collecting duct into the plasma. Consequently, these patients have a concentrated urine (urine osmolarity > 500 mOsm/kg, urine-to-plasma osmolar ratio of 2.0) and a diluted plasma (plasma osmolarity < 280 mOsm/L, serum sodium < 140 mEq/L, BUN < 15 mg/dl, and uric acid < 2 mg/dl). The reabsorption of water from the collecting duct into the plasma also results in intravascular volume expansion which causes a depression of proximal tubular sodium reabsorption and a natriuresis (urinary sodium > 50 mEq/L, FE_{Na} > 2 percent). Several aspects of this sequence of events require additional clarification: *(a)* neither the retention of water nor the quantity of sodium lost in the urine can completely account for the profound hyponatremia which may occur in some patients, and it has been proposed that some sodium enters cells where it becomes osmotically inactive [86]; *(b)* hyponatremia occurs only when excess free water has been administered and retained; conversely, if predominantly isotonic fluid is given or fluid is restricted early, hyponatremia may not occur [87]; *(c)* in the face of severe hyponatremia, urine osmolarity may not be very high but the urine will not be maximally dilute (less than 100 mOsm/L) and, therefore, is inappropriately concentrated relative to plasma osmolarity [87]. Thus, when a patient has a persistently concentrated urine despite a fall in serum sodium and osmolarity combined with an elevated urine sodium concentration, the diagnosis of non-physiologic ADH secretion should be entertained: the normal or low serum osmolarity indicates that the osmolar receptors are not stimulated and the increased urine sodium implies that intravascular volume is replete or expanded; therefore, the baroreceptors are not stimulated and, thus, the persistently concentrated urine must be the result of non-physiologic ADH secretion.

This syndrome was described first in patients with bronchogenic carcinoma [88]. Subsequently, a variety of clinical conditions have been associated with this process. In the intensive care setting, this syndrome is frequently seen in patients with pulmonary problems [89] (pneumonia, ventilator therapy), intracranial lesions [90] (tumor, trauma, meningitis), in post-operative patients [87], and secondary to drugs (vincristine, chlorpropamide, cyclophosphamide, morphine) [91]. It is important to remember that emotional stress and pain may cause the release of ADH, and in some patients no cause will be evident. The anticipation of the development of this syndrome in appropriate clinical settings has important implications for fluid therapy. In patients with meningitis, head trauma, or after general anesthesia, only one-half to two-thirds of usual maintenance fluids should be given, since it is likely that serum ADH levels will be high and, consequently, the patients will not be able to dilute their urine to specific gravity 1.010 or less.

Since the primary determinant of this syndrome is persistent reabsorption of water with consequent dilution of plasma and intravascular volume expansion, the principal mode of therapy is fluid restriction. The clinical complication of this syndrome, particularly hyponatremia, can be entirely prevented by fluid restriction even though there is persistent secretion of ADH. In fact, in most patients, fluid restriction alone is sufficient to correct hyponatremia and should be considered the basis of therapy. In cases of severe hyponatremia, hypertonic (3 percent) saline should be given to acutely raise serum sodium in order to diminish central nervous system complications such as coma or convulsions. Hypertonic saline infusion

results in additional volume expansion and diminished proximal sodium reabsorption so that the effectiveness of this therapy is transient, at best, and may result in hypertension or congestive heart failure. The combination of potent diuretic agents and hypertonic fluid infusions may be effective in patients with severe hyponatremia [92]. The diuretic agents produce urine which contains 75–100 mEq/L of sodium and chloride. Thus, the infusion of a more hypertonic solution in a volume equal to the urine output should result in an increase in serum sodium without additional volume expansion. Because of the rapid shifts in fluids and electrolytes which occur with this therapy, it should be instituted with caution. Other therapeutics have been used in patients with chronic SIADH [93], but these are rarely applicable for acutely ill patients.

Throughout this approach to the assessment of a child or adolescent with oliguria, we have emphasized the use of urinary sodium concentration and osmolarity as an integral part of the diagnostic process. In this regard, two important factors must be underscored. The urinary sodium concentration and osmolarity are a valid index of the pathophysiologic cause of oliguria only if the urine sample is obtained before the patient has been given: *(1)* a significant fluid challenge (20 cc/kg/hour) or *(2)* diuretic agents (mannitol, furosemide, ethycrinic acid). In some situations, one may not be able to differentiate the cause for the oliguria, and two manipulations can be attempted. First, assuming that the patient does not have overt evidence of fluid overload such as pulmonary or peripheral edema, a volume challenge (20 cc/kg/hour) of isotonic fluid should be administered. Since the fluid is isotonic, the potential hyponatremia associated with a fixed renal injury or non-physiologic ADH secretion should not be exacerbated and the patient with oliguria secondary to volume depletion or diminished renal perfusion should manifest an increase in urine output. Similarly, the administration of furosemide (4 mg/kg/intravenously) would be expected to result in a diuresis in patients with volume depletion but would have little or no effect for patients with ARF. It must be remembered that both of these maneuvers will invalidate the use of urinary sodium concentration, FE_{Na}, or urinary osmolarity in differentiating the cause of oliguria.

ASSESSMENT OF POLYURIA

The development of urine output which exceeds expected values (> 4 cc/kg/hour) is termed polyuria. Children are considerably more susceptible to the problems of volume overload and the development of polyuria in response to increased intravascular volume because small volumes of fluid can produce a greater degree of volume expansion in children than they can in adults. This condition requires careful evaluation and may arise from two major sources: *(1)* excretion of a fluid load or *(2)* a tubular defect for sodium and/or water reabsorption. As shown in Table 3, an assessment of the changes in the plasma values of sodium and osmolarity compared with these same values in the urine may be quite helpful in evaluating the possible causes of polyuria. In polyuric patients, the urinary concentration of sodium and osmolarity must be interpreted in the context of the sodium concentration and osmolarity of the fluids being administered to the patient. Thus, specific values for serum and urine sodium and osmolarity have not been given in Table 3, but relative changes have been indicated.

Excretion of Fluid Load

If a patient has received an excess volume of fluid which must be excreted (20 cc/kg/hour or twice maintenance fluid requirement), the patient will appear clini-

TABLE 3
Evaluation of Polyuria
(>4 cc/kg/hour)

	Serum		Urine	
	Sodium	Osmolarity	Sodium	Osmolarity
Excretion of Volume				
Hypertonic	↑	↑	↑	↑
Isotonic	↔	↔	↑	↔
Hypotonic	↓	↓	↓	↓
Tubular Defect				
$Na + H_2O$ (ATN, post-obstructive, interstitial nephritis, cystic)	↔	↔	↑	↔
H_2O only (Diabetes insipidus)	↑	↑	↓	↓

cally well hydrated and the changes in plasma and urinary constituents will depend, to some extent, on the type of fluid load which has been given. Because of concomitant expansion of the intravascular space, one would expect an increase in urinary sodium concentration and an $FE_{Na} > 1$ percent early in the course of a volume-induced diuresis irrespective of the tonicity of fluid given. If hypertonic solutions are given, plasma osmolarity would increase, ADH would be released, and a large volume of concentrated (hypertonic) urine would be excreted. If the fluid given is isotonic to plasma, the resultant diuresis would be isotonic. When hypotonic solutions are ingested, serum osmolarity falls, ADH secretion is suppressed, and a large volume of dilute urine is produced. Late in the course of excretion of a hypotonic volume load, the urine sodium concentration will fall as intravascular volume expansion is corrected. Most often, polyuria which arises from excretion of a fluid load occurs because of inadvertent or overzealous fluid therapy. In evaluating such patients, all fluids given to the patient, including intra-operative fluids, must be carefully scrutinized. Therapy for this problem is clearly to restrict fluids and allow the patient to excrete the volume load already administered.

Defect in Salt and/or Water Reabsorption

The second category of causes for polyuria is a tubular defect in salt and/or water reabsorption. In contrast to the patients who are excreting a volume load and appear clinically well hydrated, patients in this category will maintain a high urine flow rate despite appearing clinically volume-depleted. In patients with a salt-losing nephropathy, a defect in maximal urinary concentrating ability is usually also present, and these patients excrete a large volume of a urine with an increased sodium content and with an isotonic osmolarity even when intravascular volume is low or renal perfusion diminished. This type of renal tubular defect may be due to anatomic (cystic diseases, partial ureteral occlusion), pathologic (interstitial nephritis, non-

oliguric ARF, recovery phase of oliguric ARF, post-obstructive diuresis, DKA), or pharmacologic (osmotic diuresis, loop-acting diuretics, drugs) lesions. In most instances, the specific cause for the salt and water diuresis will be apparent from the associated clinical findings. The major complications associated with these causes of polyuria are related to fluid and electrolyte abnormalities, particularly hyponatremia, if urine losses are replaced with hypotonic solutions; hypokalemia and hypocalcemia occur because of the excess urinary loss of these electrolytes, and dehydration/hypotension develops because of the limited concentrating ability. Therapy is aimed at the specific cause which is identified and the replacement of fluid losses to prevent volume depletion.

Diabetes insipidus (DI) is a tubular defect in water reabsorption due to a lack of ADH release from the posterior pituitary (central DI) or a failure of the kidney to respond to ADH (nephrogenic DI) [93]. In either case, polyuria occurs because of the inability to re-claim tubular fluid presented to the collecting duct. Consequently, these patients produce a persistently dilute urine which has a low urinary sodium concentration since there is no defect in sodium reabsorption. The excretion of large volumes of dilute urine results in hypernatremia and hypertonicity of plasma. In many respects, this syndrome is defined as the inverse of non-physiologic ADH secretion: the production of a persistently dilute urine despite increasing serum sodium and osmolarity. Central DI may result from an injury to the posterior pituitary where ADH is stored or the hypothalamus where ADH is produced. Central DI has been associated with head trauma, meningitis, tumors, and cerebral edema. Since the renal tubule is intact, these patients respond to ADH or one of its analogs, 1-desamine-8D-arginine vasopressin (dDAVP), by producing a concentrated urine. When central DI is fully established, it is difficult to administer sufficient fluids to maintain the patient in a homeostatic state, and ADH should be given. Care must be taken to adjust fluids appropriately once ADH is effective to avoid wide and rapid swings in serum sodium. Because of greater dependability, aqueous pitressin or dDAVP are preferred to pitressin tannate in oil. dDAVP can be used only if the nasopharyngeal mucosa is intact.

Nephrogenic DI results in the same perturbations in serum and urine sodium and osmolarity as may be seen in patients with central DI [93]. Patients with nephrogenic DI have a tubular insensitivity to ADH which may be either hereditary or secondary to drugs [82] (methoxy-flurane, propoxyphene, lithium, or demethyl-chlortetracycline), renal parenchymal disease (chronic glomerulonephritis, sickle cell nephropathy), or electrolyte abnormalities (hypokalemia or hypercalcemia). Therapy should be directed toward elimination of the secondary causes of nephrogenic DI when possible and reduction in the renal solute load to diminish the degree of diuresis. Patients with the sex-linked hereditary disorder will require management with diuretics or prostaglandin synthetase inhibitors.

This article has outlined an approach to the assessment of critically ill children who have developed disorders of urine output. We have emphasized an understanding of the pathophysiology of salt and water excretion by the kidney as a foundation to the diagnosis and management of patients with oliguria and polyuria. Based on this approach, the causes of disorders of urine output should be readily diagnosed and effectively treated.

REFERENCES

1. Navar LG: Renal autoregulation: perspectives from whole kidney and simple nephron studies. Am J Physiol 234:357, 1978

2. Schwartz GH, Haycock GB, Spitzer A: Plasma creatinine and urea: normal values. J Peds 88:828, 1976
3. Schwartz GJ, Haycock GB, Edelmann CM, et al: A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Peds 58(2):259, 1976
4. Nash MA: Water and solute homeostasis. In Pediatric Kidney Disease. Edited by CA Edelman. Boston, Little, Brown & Co, 1978
5. Ellenbogen PH, Scheible FW, Talner LB, et al: Sensitivity of gray scale ultrasound in detecting urinary tract obstruction. Am J Roent 130:731, 1978
6. Sander RC, Jeck DL: B-scan ultrasound in the evaluation of renal failure. Radiology 119:199, 1976
7. Norman ME, Asadi FK: A prospective study of acute renal failure in the newborn infant. Peds 63(3):475, 1979
8. Cameron JS, Dick RM, Ogg CS, et al: Plasma C_3 and C_4 concentrations in the management of glomerulonephritis. Br Med J 3:668, 1973
9. Dodge WF, Spargo BH, Bass JA, et al: The relationship between the clinical and pathologic features of poststreptococcal glomerulonephritis. A study of the early natural history. Med 47:277, 1968
10. Dodge WF, Spargo BH, Travis LB, et al: Poststreptococcal glomerulonephritis. A prospective study in children. New Eng J Med 268:273, 1972
11. Lewy JE, Salinas-Madrigal L, Herdson PB, et al: Clinico-pathologic correlations in acute poststreptococcal glomerulonephritis: A correlation between renal functions, morphologic damage and clinical course of 46 children with acute poststreptococcal glomerulonephritis. Med 50:453, 1971
12. Travis LB, Dodge WF, Beathard GA, et al: Acute glomerulonephritis in children. A review of the natural history with emphasis on prognosis. Clin Nephrol 1:169, 1973
13. Jordan SC, Lemire JM: Acute glomerulonephritis: diagnosis and treatment. Ped Clin North Am 29:857, 1982
14. Dolislager D, Tune B: The hemolytic-uremic syndrome. Spectrum of severity and significance of prodrome. Am J Dis Child 132:55, 1978
15. Fong JSC, de Chadarevian JP, Kaplan BS: Hemolytic-uremic syndrome. Current concepts and management. Ped Clin North Am 29:835, 1982
16. Gasser C, Gauthier E, Steck A, et al: Hamolytisch-uramische syndrome: Bilaterale nierenrindennekrosen bei akuten erworbenen hamolytischen anamien. Schweiz Med Wochensch 38:905, 1955
17. Tune BM, Leavitt TJ, Gribble TJ: The hemolytic-uremic syndrome in California: a review of 12 nonheparinized cases with long-term follow-up. J Peds 82:304, 1973
18. Upadhaya K, Barwick K, Fishaut M, et al: The importance of non-renal involvement in hemolytic uremic syndrome. Peds 65:115, 1980
19. Finn WF, Arendshorst WJ, Gottschalk CW: Pathogenesis of oliguria in acute renal failure. Circ Res 36:675, 1976
20. Kashgarian M: Acute Renal Failure. Pathology Annual 15:335, 1980
21. Oken DE: On the passive back flow theory of acute renal failure. Am J Med 58:77, 1975
22. Stein JH, Lifschitz MD, Barnes LD: Current concepts on the pathophysiology of acute renal failure. Am J Physiol 234:F171, 1978
23. Oken DE: Acute renal failure (vasomotor nephropathy) Micropuncture studies of the pathogenetic mechanisms. Ann Rev Med 307:319, 1975
24. Siegel NJ, Gunstream SK, Handler RI, et al: Renal function and cortical blood flow during the recovery phase of acute renal failure. Kidney Int 12:199, 1977
25. Donohoe JF, Venkatachalam MA, Bernard DB, et al: Tubular leakage and obstruction after renal ischemia: Structural-functional correlations. Kidney Int 13:208, 1978
26. Gaudio KM, Taylor MR, Chaudry IH, et al: Accelerated recovery of single nephron function by the postischemic infusion of ATP-$MgCl_2$. Kidney Int 22:13, 1982
27. Myers BD, Chui F, Hilberman M, et al: Transtubular leakage of glomerular filtrate in human acute renal failure. Am J Physiol 237(4):319, 1979
28. Safirstein R, Miller P, Dikman S, et al: Cisplatin nephrotoxicity in rats: Defect in papillary hypertonicity. Am J Physiol 241:F175, 1981
29. Venkatachalem MA, Bernard DB, Donohue JF, et al: Ischemic damage and repair in the rat proximal tubule: Differences among the S_1, S_2, and S_3 segments. Kidney Int 14:31, 1978
30. Arendshorst WJ, Finn WF, Gottschalk CW: Micropuncture study of acute renal failure following temporary renal ischemia in the rat. Kidney Int 10:S100, 1976
31. Finn WF, Chevalier RL: Recovery from postischemic acute renal failure in the rat. Kidney Int 16:113, 1979
32. Tanner GA, Sophasen S: Kidney pressure after temporary renal artery occlusion in the rat. Am J Physiol 230:1173, 1976

33. Tanner GA, Steinhausen M: Tubular obstruction in ischemia-induced acute renal failure in the rat. Kidney Int 10:S65, 1976
34. Solez K, Morel-Maroger L, Sraer JD: The morphology of "acute tubular necrosis" in man: Analysis of 57 renal biopsies and a comparison with the glycerol model. Med 58(5):362, 1979
35. Anand SK, Northway JD, Crussi FK: Acute renal failure in newborn infants. J Peds 92:985, 1978
36. Dauber IM, Krauss AN, Symchych PS, et al: Renal failure following perinatal hypoxia. J Peds 88:851, 1976
37. Gianantonio CA, Vitacco M, Mendilaharza J, et al: Acute renal failure in infancy and childhood. J Peds 61:660, 1962
38. Gordillo-Paniagua G, Velasquez-Jones L: Acute renal failure. Ped Clin North Am 23(4):817, 1976
39. Reimold EK, Don TD, Worthen HG: Renal failure during the first year of life. Peds 59:987, 1977
40. Appel GB, Siegel NJ, Appel AS, et al: Studies on the mechanism of non-oliguric experimental acute renal failure. Yale J Bio Med 54:273, 1981
41. Henry LN, Lane CE, Kashgarian M: Micropuncture studies of the pathophysiology of acute renal failure in the rat. Lab Invest 19:309, 1968
42. Anderson RJ, Linas SL, Berns AS, et al: Non-oliguric acute renal failure. New Eng J Med 296:1134, 1977
43. Appel GB, Neu HC: The nephrotoxicity of antimicrobial agents. New Eng J Med 296:663, 772, 784, 1977
44. Minuth AN, Terrell JB Jr, Suki WN: Acute Renal Failure: A study of the course and prognosis of 104 patients and the role of furosemide. Am J Med Sci 271:317, 1976
45. Tune BM, Fravert D: Mechanisms of cephalosporin nephrotoxicity: A comparison of cephaloridine and cephaloglycin. Kidney Int 18:591, 1980
46. Wardle EN: Endotoxin and acute renal failure. Nephron 14:321, 1975
47. Bidani A, Churchill P, Fleischmann L: Sodium-chloride-induced protection in nephrotoxic acute renal failure: Independence from renin. Kidney Int 16:481, 1979.
48. Cox JW, Baehler RW, Sharma H, et al: Studies on the mechanism of oliguria in a model of unilateral acute renal failure. J Clin Invest 53:1546, 1974
49. Cronin RE, DeTorrente A, Miller PD, et al: Pathogenic mechanisms in early norepinephrine-induced acute renal failure: Functional and histological correlates of protection. Kidney Int 14:115, 1978
50. Wilson DR, Thiel G, Arce ML, et al: The role of concentrating mechanism in the development of acute renal failure: Micropuncture studies using diabetes insipidus rats. Nephron 6:128, 1969
51. Thiel G, Brunner F, Wunderlich P, et al: Protection of rat kidneys against $HgCl_2$ induced acute renal failure by induction of high urine flow without renin suppression. Kidney Int 10:S191, 1976
52. Barry KG: Post traumatic renal shutdown in humans: Its prevention and treatment by the intravenous infusion of mannitol. Milit Med 128:224, 1963
53. Etheredge EE, Levitin H, Nakamura K, et al: Effect of mannitol on renal function during open-heart surgery. Ann Surg 161:53, 1965
54. Teschan PE, Lawson NL: Studies in acute renal failure: Prevention by osmotic diuresis, and observations on the effect of plasma and extracellular volume expansion. Nephron 3:1, 1966
55. Tiller DJ, Mudge GH: Pharmacologic agents used in the management of acute renal failure. Kidney Int 18:700, 1980
56. Kjellstrand CM: Ethacrynic acid in acute tubular necrosis: indication and effect on the natural course. Nephron 9:337, 1972
57. Bia MJ, DeFronzo RA: Extrarenal potassium homeostasis. Am J Physiol 240:F257, 1981
58. Siegel NJ, Mulrow PJ: The management of hypertension. In Pediatric Kidney Disease. Edited by CA Edelman. Boston, Little, Brown & Co, 1978
59. Loggie JM: Hypertension in children and adolescents. II. Drug therapy. J Peds 74:640, 1969
60. McLaine PN, Drummond KN: Intravenous diazoxide for severe hypertension in childhood. J Peds 79:829, 1971
61. Pruitt AW, Boles A: Diuretic effect of furosemide in acute glomerulonephritis. J Peds 89(2):306, 1976
62. Palmer RF, Lasseter K: Sodium nitroprusside. New Eng J Med 292:294, 1975
63. Mauer SM, Lynch RE: Hemodialysis techniques for infants and children. Ped Clin North Am 23(4):843, 1976
64. Siegel NJ, Glazier WB, Chaudry IH, et al: Enhanced recovery from acute renal failure by the postischemic infusion of adenine nucleotides and magnesium chloride in rats. Kidney Int 17:338, 1980
65. Siegel NJ: Amino acids and adenine nucleotides in acute renal failure. In: Acute Renal Failure. Edited by BM Brenner, JM Lazarus, BD Myers. In press

66. Toback FG: Amino acid treatment of acute renal failure. Contemporary Issues in Nephrology No 6. Acute Renal Failure. Edited by B Brenner, J Stein. New York, Churchill Livingston, 1980
67. Lee HA, Sharpstone P, Ames AC: Parenteral nutrition in renal failure. Postgrad Med J 43:81, 1967
68. Abel RM, Abbott WM, Fischer JE: Acute Renal Failure. Treatment without dialysis by total parenteral nutrition. Arch Surg 103:513, 1971
69. Abel RM, Abbott WM, Fischer JE: Intravenous essential L-amino acids and hypertonic dextrose in patients with acute renal failure. Effects on serum potassium, phosphate and magnesium. Am J Surg 123:632, 1972
70. Wilmore DW, Dudrick SJ: Treatment of acute renal failure with intravenous essential L-amino acids. Arch Surg 99:669, 1969
71. Abel RM, Beck CH Jr, Abbott WM, et al: Improved survival from acute renal failure after treatment with intravenous essential L-amino acids and glucose. Results of a prospective double-blind study. New Eng J Med 288:695, 1973
72. Baek SM, Madabali GG, Bryan-Brown CW, et al: The influence of parenteral nutrition on the course of acute renal failure. Surg Gyn Obst 141:405, 1975
73. Leonard CD, Luke RG, Siegel RR: Parenteral essential amino acids in acute renal failure. Urology 6:154, 1975
74. Abel RM, Abbott WM, Beck CH Jr, et al: Essential L-amino acids for hyperalimentation in patients with disordered nitrogen metabolism. Am J Surg 128:317, 1974
75. Brown CB, Ogg CS, Cameron JS: High dose furosemide in acute renal failure: a controlled trial. Clin Neph 15(2):90, 1981
76. Kleinknecht D, Ganeval D, Gonzalez-Duque LA, et al: Furosemide in acute oliguric renal failure: a controlled trial. Nephron 17:51, 1976
77. Hall JW, Johnson WJ, Maher FT, et al: Immediate and long-term prognosis in acute renal failure. Ann Int Med 73:515, 1970
78. Lewers DT, Mathew TH, Maher JF, et al: Long-term follow-up of renal function and histology after acute tubular necrosis. Ann Int Med 73:523, 1970
79. Hollenberg NK, Epstein M, Rosen SM, et al: Acute oliguric renal failure in man: evidence for preferential renal cortical ischemia. Med 47:455, 1968
80. Kashgarian M, Siegel NJ, Ries AL, et al: Hemodynamic aspects in development and recovery phases of experimental postischemic acute renal failure. Kidney Int 10:S160, 1976
81. Hsu CH, Preuss HG, Argy WP, et al: Prolonged tubular malfunction following acute oliguric renal failure. Nephron 13:342, 1974
82. Verney EB: The antidiuretic hormone and the factors which determine its release. Proc Roy Soc 135:25, 1947
83. Johnson JA, Zehr JE, Moore WW: Effects of separate and concurrent osmotic and volume stimuli on plasma ADH in sheep. Am J Physiol 218:1273, 1970
84. Share L: Vasopressin, its bioassay and the physiological control of its release. Am J Med 42:701, 1967
85. Johnson JA, Moore WW, Segar WE: Small changes in left atrial pressure and plasma antidiuretic hormone titers in dogs. Am J Physiol 217:210, 1969
86. Bartter FC, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790, 1967
87. Mendoza SA: Syndrome of inappropriate antidiuretic hormone secretion (SIADH). Ped Clin North Am 23(4):681, 1976
88. Schwartz WB, Bennett W, Curelop S, et al: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 23:529, 1957
89. Mor J, Ben-Galim E, Abrahamov A: Inappropriate antidiuretic hormone secretion in an infant with severe pneumonia. Am J Dis Child 129:133, 1975
90. Kaplan A, Feigin R: Inappropriate secretion of antidiuretic hormone in meningitis. J Peds 92(5):758, 1978
91. Friedman AL, Segar WE: Medical Progress. Antidiuretic hormone excess. J Peds 94:521, 1979
92. Hantman D, Rossier B, Zohlman R, et al: Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. An alternative treatment to hypertonic saline. Ann Int Med 78:870, 1973
93. Singer I, Forrest JN Jr: Drug-induced states of nephrogenic diabetes insipidus. Kidney Int 10:82, 1976