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Tumor lysis syndrome: pathogenesis and management

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Abstract. Tumor lysis syndrome refers to the metabolic disturbances (hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia) associated with lymphoproliferative malignancies which occur secondary to cell lysis. In some patients, tumor lysis results in acute renal failure. The nature and severity of the metabolic alterations are variable and may be influenced by the timing and intensity of chemotherapy, the magnitude of cell lysis, and the general condition of the patient with respect to hydration and glomerular filtration rate. Not only do hyperuricemia and hyperphosphatemia result from tumor lysis syndrome, they also contribute to oliguric acute renal failure in patients with tumor lysis. The pathogenesis of tumor lysis syndrome and current therapeutic strategies are discussed.

Key words: Tumor lysis syndrome – Acute renal failure – Hyperphosphatemia – Hyperuricemia – Dialysis – Hemofiltration

Introduction

Tumor lysis syndrome comprises a number of metabolic abnormalities (hyperuricemia, hyperphosphatemia, hyperkalemia, azotemia, and hypocalcemia) which are associated with lymphoproliferative malignancies following spontaneous or chemotherapy-induced cytolysis. The most commonly associated malignancies are non-Hodgkin's lymphoma and acute lymphocytic leukemia. The nature and severity of the metabolic alterations encountered in the cancer patient with tumor lysis are influenced by: (1) the timing and intensity of chemotherapy; (2) the magnitude of intracellular ion and solute release, including that of urate precursors, phosphates, and potassium; (3) prophylactive measures such as hydration; (4) acid-base status; (5) glomerular filtration rate (GFR). Not only do hyperuricemia and hyperphosphatemia result from tumor lysis syndrome, they also contribute to oliguric acute renal failure in patients with tumor lysis. This review provides basic background information concerning tumor lysis syndrome, discusses current theories of pathogenesis, and presents preventive as well as therapeutic strategies.

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Risk factors for development of acute renal failure in tumor lysis syndrome

Of the metabolic abnormalities accompanying tumor lysis syndrome, elevated uric acid, phosphate, and other purine metabolite levels have been implicated as causes of acute renal failure. Hyperuricemia is the single most common finding in patients with tumor lysis syndrome and acute renal failure. In a series reported by Cohen et al. [1], 15 of 46, or 33%, of patients with Burkitt's lymphoma had uric acid levels greater than 8.0 mg/dl prior to initiation of chemotherapy. However, in all but 2 patients who required dialysis for hyperuricemia before chemotherapy could be started, the serum uric acid levels responded to allopurinol therapy and forced diuresis. As expected, hyperuricemia was more likely to be present in azotemic patients compared with nonazotemic patients, as was hyperphosphatemia, hypocalcemia, and hyperkalemia. The size of the tumor burden, as well as reduced GFR prior to chemotherapy, were somewhat predictive of renal insufficiency, since the patients who experienced renal failure tended to have higher lactate dehydrogenase (LDH) values and evidence of delayed excretion of contrast on intravenous pyelogram; however, pretreatment uric acid levels were comparable to patients who did not experience renal failure. Of note, the contrast administered to these patients could have contributed to the acute renal failure, since radiocontrast material itself can precipitate renal failure as well as reduce renal excretion of uric acid.

Of 40 cases of B cell lymphoma reported by Stapleton et al. [2], 10 experienced acute renal failure secondary to tumor lysis syndrome and of these, 2 presented with acute renal failure prior to the initiation of chemotherapy. All children had received the benefit of allopurinol and forced diuresis prior to initiation of chemotherapy. There was no recognizable difference in clinical stage, age, gender, or incidence of elevated uric acid, creatinine, calcium, or phosphorus levels prior to initiation of chemotherapy in the azotemic versus nonazotemic group. The mean levels of uric acid, phosphorus, and LDH tended to be higher in the azotemic group, but these differences did not reach statistical significance. Urinary volume was an important factor distinguishing those children who required dialysis from those who did not. Hyperuricemia was the major contributing factor attributed by the authors to cause acute renal insufficiency in 4 of these patients, and probably contributed to renal failure in 2 or 3 others. Hyperphosphatemia was suspected as the major immediate cause of renal failure in 2 patients.

From the series reported by Cohen et al. [1] and Stapleton et al. [2], the presence of hyperuricemia did not necessarily predict which patients experienced acute renal failure. However, there is a clear association between hyperuricemia and renal insufficiency at the time of diagnosis of the malignancy [3, 4]. In fact, the presence of hyperuricemic acute renal insufficiency may be the primary clue to the presence of occult lymphoproliferative malignancy [4]. Jones et al. [4] described three children who presented with acute renal failure and hyperuricemia who were found to have acute lymphoblastic leukemia (ALL), yet had not manifest symptoms suggestive of leukemia prior to diagnosis. Kjellstrand et al. [3] presented 16 cancer patients with hyperuricemic acute renal failure: 5 of the 16 patients had hyperuricemic acute renal failure prior to chemotherapy, and 4 of the remaining 11 had hyperuricemia after prednisone alone. In addition, hyperphosphatemia out of proportion to the degree of renal insufficiency was present, particularly in those patients who developed renal failure after chemotherapy was initiated rather than those who presented with hyperuricemia and azotemia prior to chemotherapeutic agents.

Although hyperuricemia is the single most important clinical finding in patients with tumor lysis syndrome who develop acute renal failure, some patients never experience hyperuricemia (or hyperuricosuria). Other potential causes for renal insufficiency in patients with lymphoproliferative malignancies are hyperphosphatemia, xanthinuria, infiltration of renal parenchyma by malignant cells, intra- or extramural ureteric obstruction, vascular diseases, concomitant nephrotoxic drugs, and intravascular volume depletion [4]. Hyperphosphatemia is under emphasized as a potential cause of oliguria and filtration failure. Elevated plasma phosphorus is a consistent finding in tumor lysis syndrome, especially in those who require dialysis [5–7]. Indeed, in some instances the measures aimed at preventing or reducing hyperuricemia may predispose the patient to phosphate-related renal disease. Overzealous alkalinization of urine may lead to massive phosphate crytalluria because phosphate precipitates at alkaline pH [2].

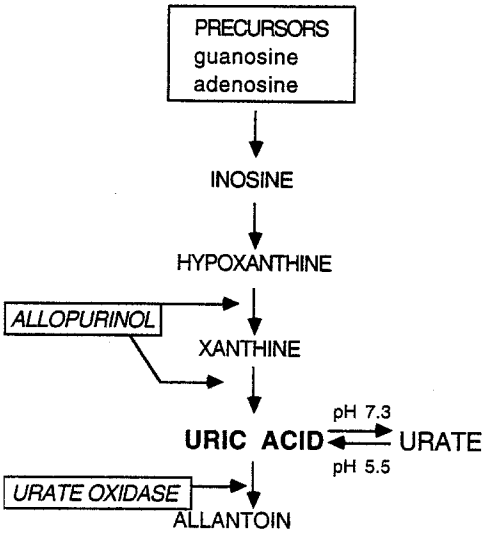

Fig. 1. Metabolic pathway for uric acid

Allopurinol lowers uric acid production and is standard therapy for nearly all patients with lymphoid malignancies. It inhibits xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to uric acid (Fig. 1) and has been associated with increased plasma and urinary levels of hypoxanthine and xanthine. Xanthine, which may precipitate in a manner similar to that of uric acid, is actually less soluble than uric acid and may also cause acute renal failure [8]. Andreoli et al. [9] studied 19 children with acute lymphocytic leukemia who received allopurinol and developed tumor lysis syndrome; 4 of these children developed acute renal failure [hemodialysis in 2, peritoneal dialysis (PD) in 2]. Urinary uric acid excretion increased in all children during tumor lysis, with the mean level increasing from 447 ± 251 μg/dl glomerular filtrate before chemotherapy to 778 ± 463 μg/dl after initiation of therapy. In addition, excretion of both xanthine and hypoxanthine increased dramatically. Plasma xanthine levels were significantly elevated in 3 of the patients with acute renal failure compared with 6 children without acute renal failure. Urinary excretion of xanthine was higher in children requiring dialysis compared with those who did not experience renal failure. However, the peak urinary concentrations were not different among the two groups. Xanthine crystals were detected in 8 (6/15 without renal failure and 2/4 with) and was associated with urinary xanthine levels greater than 350 mg/l. The urinary excretion of purine metabolites was positively correlated with the initial uric acid concentration. The authors concluded that acute renal failure was not related to the peak urinary concentrations of purine metabolites or the presence of xanthine crystalluria. However, the urinary excretion of uric acid, hypoxanthine, and xanthine was greater in those who developed renal insufficiency. The authors postulated that the plasma level of xanthine present in the vasa recta might predispose to medullary sludging, a possible mechanism for renal insufficiency in this setting.

Pathogenesis of nephropathy in tumor lysis syndrome

Hyperuricemia

Renal clearance of uric acid in humans approximates 10% of GFR, or 8.7±2.5 ml/min [10]. Urate is almost completely filtered at the glomerulus and is minimally protein bound. Of the urate filtered, 95%–99% is reabsorbed by the early proximal tubule; uric acid secretion, the main source of excreted uric acid, occurs at a site distal to the early reabsorptive process. Further reabsorption of uric acid may occur at a site distal to the secretory site; however, this process is poorly understood. A uric acid gradient is present from cortex to medulla, and parallels the increasing urinary concentration of uric acid as one travels distally to the collecting duct where the urinary uric acid concentration is highest.

In the presence of hyperuricemia, renal uric acid excretion increases. Renal excretion of uric acid is supranormal in normouricemic as well as hyperuricemic patients with lymphoid malignancies [11, 12]. Urinary uric acid excretion is higher in leukemic individuals than in normal individuals with comparable serum uric acid levels [12]. Although patients with acute myoblastic leukemia do not typically experience tumor lysis syndrome, uric acid production is high and urinary excretion is approximately 3 times normal prior to chemotherapy and 6 times normal post treatment. Increased basal production of uric acid and lysis of tumor cells increases the filtered load of uric acid. When the excretory capacity of the renal tubule is exceeded, hyperuricemia occurs. As noted above, elevated urinary uric acid levels have been reported in the presence of normal plasma uric acid levels. Uric acid crystals form in the presence of an acidic pH, whereas monosodium urate or monosodium monohydrate urate crystals form at physiological pH. In leukemia, the predominant form of crystals deposited within the kidney is uric acid, in contrast to individuals with gout who tend to form urate crystal deposits.

Most human pathology of urate nephropathy is from autopsy specimens and therefore limited to the more severe cases [13, 14]. Uric acid deposits are found within the lumina of renal tubules, particularly the collecting ducts. A peritubular granulomatous reaction may be observed. Phagocytosis of uric acid crystals by renal tubular epithelial cells has also been suggested by the presence of crystals in the lysosomes or cytosol. Uric acid crystals were observed in the collecting ducts and deep cortical and medullary vessels. There are several reasons why uric acid tends to deposit in these areas of the kidney: the presence of renal concentration of intraluminal fluid, acidic pH of distal tubular fluid, decreased tubular flow rates, and hemoconcentration in medullary vessels [10, 13, 14]. Thus, urinary uric acid concentrations increase as one travels distally at the level of the distal tubule, where urinary pH drops leading to a greater fraction of molecules in their less-soluble form [10, 13].

Pathophysiology of uric acid-induced renal failure

The primary functional abnormality leading to azotemia/oliguria in urate nephropathy is intraluminal tubular obstruction; vascular obstruction may also contribute to filtration failure. Massive quantities of purines, metabolites, phosphates, and other intracellular constituents not only herald the onset of tumor lysis but also contribute to filtration failure by forming crystals or precipitates within the renal tubules and microvessels. One might anticipate that the urinary rather than plasma levels of urate are more important in the pathogenesis of urate nephropathy. Indeed, most studies have demonstrated a poor correlation of plasma uric acid levels with the degree of renal dysfunction.

Renal functional studies performed in 26 patients with leukemia revealed that 86% of inulin clearance studies were normal in patients with normal plasma uric acid levels (<6.5 mg/dl) compared with only 18% normal clearance studies in patients with hyperuricemia [11]. Hyperuricemia was accompanied by an increase in the rate of uric acid excretion as well as an increase in urinary uric acid concentration. In general, patients with urinary uric acid concentrations of greater than two standard deviations above the normal mean had decreased inulin clearances. Decreased GFR alone did not account for the high urinary uric acid concentrations or the higher than normal urinary uric acid clearances, since chronic renal failure patients with equivalent decreases in GFR and mild hyperuricemia did not exhibit increased uric acid clearances [11]. Interestingly, the only patients with hyperuricemia who had normal inulin clearances had received intravenous hydration for 24–48 h prior to clearance studies.

In summary, leukemia is characterized by higher urinary uric acid clearances for any given level of plasma uric acid or any level of GFR. Moreover, the urinary uric acid levels are more likely to determine the severity of the filtration failure or oliguria because of the direct correlation of urinary concentration with precipitation of uric acid – the mechanical nature of the lesion.

Urinary alkalinization, adequate hydration, and forced diuresis are employed to increase the solubility of uric acid thus reducing the likelihood of precipitation. To determine the relative contributory effects of tubular fluid flow rate, urine pH, and urine osmolality on the severity of urate nephropathy, rats with hyperuricemia were treated with one of the following: alkalinization of urine, acid urine and moderate diuresis, and high-flow solute diuresis and high-flow water diuresis [15]. Both tubular and vascular obstruction were observed with decreased renal blood flow (RBF) and GFR. Increasing urine flow rate was the most effective method for preventing the reduction in RBF and GFR. Some preservation of GFR occurred in animals treated with moderate diuresis in the absence of urinary alkalinization. High distal tubular fluid flow rate reduced the distal tubular concentration of uric acid, allowing greater solubility and forcing urate deposits out of the tubules. Urinary urate concentration was inversely related to urine flow rate and indirectly correlated with the degree of renal protection. Urinary pH of 7.0 in the absence of forced diuresis was not particularly effective in preventing urate deposition in tubules and vessels.

Hyperphosphatemia

Hyperphosphatemia is another metabolic alteration observed with tumor lysis syndrome that may be an etiological factor in acute renal failure [5–7, 16–18]. One study reported an incidence of 31% in nonazotemic patients and of 100% in azotemic patients with Burkitt's lymphoma [1]. Zusman et al. [16] studied the urinary phosphate clearances in six children with leukemia. Hyperphosphatemia, hypocalcemia, and hyperphosphaturia were observed within 24–48 h of the start of chemotherapy. Tubular reabsorption of phosphate decreased to 20%–70% of baseline and phosphate clearances increased to 3–24 times that of baseline measurements with modest increases in plasma phosphorus and normal creatinine clearances. Symptomatic hypocalcemia occurred in half of the patients. Sporadic cases of acute filtration failure due to hyperphosphatemia are found in the literature [5–7, 16–18], including one case of a suspected renal calculi as the etiology of transient renal insufficiency [17].

Hypocalcemia may accompany hyperphosphatemia and probably results from tissue precipitation of calcium phosphate. Treatment of hypocalcemia in a hyperphosphatemic individual may produce metastatic calcification, including intrarenal calcification, in the form of nephrocalcinosis or nephrolithiasis. Additional mechanisms have been proposed for altered calcium homeostasis in hyperphosphatemic oncology patients. Hypocalcemia may also be the result of an inadequate increase in renal proximal tubular activity of 1α-hydroxylase and thus inappropriately low 1,25-dihydroxyvitamin D_3 levels. Tumor lysis syndrome is associated with decreased proximal tubular reabsorption of phosphate, presumably through the increased parathyroid hormone levels induced by hypocalcemia [16]. Thus these patients have increased urinary excretion of phosphate which increases the risk for nephrocalcinosis or tubular obstruction from precipitation of calcium phosphate. Metabolic acidosis may induce a shift of intracellular phosphate into the extracellular space, further increasing the plasma phosphate concentrations and the filtered load of phosphate. Administration of sodium bicarbonate for urinary alkalinization may also predispose the patient to the urinary precipitation of calcium phosphate, which is less soluble at an alkaline pH. In addition, administration of alkali decreases the ionized fraction of calcium, potentially aggravating hypocalcemic symptoms. Treatment of hypocalcemia in the face of significant hyperphosphatemia should be reserved for the symptomatic patient. Phosphate binders, as well as insulin and glucose, are therapeutic options for treatment of hyperphosphatemia and hypocalcemia.

Therapy for tumor lysis syndrome

Unquestionably, the early preventative measures have been effective in reducing the morbidity and mortality associated with tumor lysis syndrome [19]. Because many of the patients with malignancies are unable to maintain adequate fluid intake they are commonly volume depleted upon medical evaluation. This is a major risk factor in the development of tumor lysis syndrome. Therefore, vigorous hydration may correct electrolyte disturbances, improve intravascular volume, increase RBF, GFR, and urine volume and thereby prevent the need for dialysis (Table 1).

Table 1. Management of tumor lysis syndrome

Hydration	D51/4 NS + 35 mEq $NaHCO_3$/l, 3 l/m^2 per day
Alkalinization	Maintain urine pH 6.5–7.0 Withdraw bicarbonate if blood level >30 mEq/l or urine pH >7.3 Consider acetazolamide (5 mg/kg per day)
Diuresis (Avoid in the face of hypovolemia)	Mannitol (0.5 g/kg IV every 6–8 h) Furosemide (1–2 mg/kg IV every 6–8 h)
Reduce uric acid	Allopurinol (10 mg/kg per day divided t.i.d., maximum 800 mg/day) Urate oxidase (100 U/kg per day IV or IM)

$NaHCO_3$, Sodium bicarbonate; t.i.d., three times a day; NS, normal saline

Allopurinol is administered to inhibit uric acid formation, and urine pH is adjusted to 6.5–7.0 to increase the solubility of uric acid (Table 1). One must avoid overzealous alkalinization which may magnify the clinical symptoms of hypocalcemia by shifting ionized calcium to its nonionized form. We recommend withdrawal of sodium bicarbonate when serum levels reach 30 mEq/l and/or urine pH is greater than 7.5. If urinary alkalinization is not achieved with elevated serum bicarbonate levels, then acetazolamide may be added to reduce proximal tubular bicarbonate reabsorption and to alkalinize the urine. Although diuretics and mannitol are commonly used to maintain adequate urinary flow, they may actually contribute to the intratubular precipitation of urate as well as calcium phosphate in the volume-contracted patient. We reserve diuretics for children in whom adequate hydration is documented and urine volume is less than 65% of intake in the absence of excessive extrarenal fluid losses (vomiting, diarrhea).

Uricase (urate oxidase, uricozyme)

Uricase converts uric acid to the water-soluble metabolite allantoin, thereby lowering plasma uric acid levels as well as urinary uric acid excretion. It does not alter the metabolism of other purine metabolites [20] and is extracted from *Aspergillus flavos* (Sanofi Winthrop Laboratories, France). Although widely used in Europe for the last 2 decades to treat hyperuricemia, it is not yet licensed for use in the United States. Uricase is administered by intramuscular injection or intravenous infusion at a dose range between 50 and 100 U/kg. An Italian study randomized patients between allopurinol and uricase at low (500 U/day) and high doses (1,000 U/day). Plasma uric acid levels fell in both groups, but the decrease was much more marked in the uricase group, reaching statistical significance by the 2nd day of therapy. No difference was observed between the children who received 500 U/day and 1,000 U/day and no side effects of the therapy were recognized.

The enzyme is currently under investigational clinical trials at St. Jude Children's Research Hospital, Memphis. It is administered intravenously over 30 min at a dose of 100 units/kg per day for 5 days following diagnosis of ALL. It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because it induces hemolysis secondary to its oxidant effect. It is to be avoided during pregnancy. Preliminary results in 14 patients with ALL are encouraging. Serum uric acid levels fell within 6 h of initiating therapy. The mean uric acid concentration pre first dose was 5.1 mg/dl (range 1.8–12.3 mg/dl) and promptly decreased to a mean of 0.6 mg/dl (range <0.5 mg/dl–1.4 mg/dl) within a few hours of the first intravenous dose. Blood samples should be placed on ice and assayed within 1 h because uricase remains active at room temperature and therefore might continue to degrade uric acid leading to falsely low values.

Uricase has also been covalently linked to PEG (monomethoxy-polyethylene glycol) in an attempt to decrease immunogenicity and increase its half-life [21]. PEG-uricase was administered at an initial dose of 1.0 U/kg intramuscularly and increased to 2 U/kg with subsequent doses. Mean uric acid levels decreased from 15 mg/dl to less than 9 mg/dl. PEG-uricase was administered by intravenous injection to five normal adults and lowered their plasma urate levels within 1 h, an effect which persisted for 36 h [22].

Dialysis

The length of oliguria prior to the initiation of dialysis appears to correlate with the length of oliguria post dialysis [19, 23]; this supports early dialysis with onset of oliguria in patients with tumor lysis. Indications for dialysis in the setting of tumor lysis syndrome are listed in Table 2. Certainly, marked oligoanuria in the face of metabolic perturbations requires immediate initiation of dialysis. When only hyperuricemia and/or hyperphosphatemia are present, the degree of oliguria and timing of chemotherapy may modify the decision for dialytic therapy. One may attempt to reduce serum phosphate or uric acid with medical therapies before proceeding with dialysis. Correction of any acid-base disturbances as well as normalization of fluid balance is of utmost importance and may prove beneficial in correcting the uric acid, phosphate, potassium, and calcium levels, as well as restoring urinary flow.

When vigorous conservative measures are unsuccessful at normalizing electrolytes or establishing urinary flow, dialysis may be necessary. There are two major goals of dialysis in the setting of tumor lysis syndrome: (1) normalization of uric acid or phosphate levels by rapid removal to treat obstructive nephropathy; (2) treatment of acute renal failure and any accompanying metabolic problems such as hyperkalemia, acidosis, hypocalcemia, and azotemia. Hemodialysis, PD, and continuous hemofiltration (arteriovenous and venovenous) with and without dialysis [continuous arteriovenous hemofiltration/hemodiafiltration (CAVH, CAVHD), continuous venovenous hemofiltration/hemodiafiltration (CVVH, CVVHD)] have been used in the treatment of both children and adults with tumor lysis syndrome. Unfortunately, data comparing the various dialysis modalities are sparse.

Table 2. Indications for dialysis in tumor lysis syndrome

Hyperkalemia
Volume overload
Hyperphosphatemia
Hypocalcemia
Hyperuricemia
Control of uremia

The major advantage of hemodialysis is that electrolyte and mineral alterations, especially life-threatening situations such as hyperkalemia and hypocalcemia, are rapidly corrected. Treatment time is usually short although dialysis may be required every 12 h until renal function and urinary volume are restored. Stapleton et al. [2] treated ten children with hemodialysis and reported return of adequate renal function in some patients following only two treatments. Uric acid and phosphate levels immediately decrease, with associated increases in urine output [3].

PD was at one time the modality of choice, however the use of hollow-fiber filters soon replaced PD due to the higher uric acid clearances reported. Although PD is an excellent choice of therapy in many forms of acute renal failure, it is not without major risks for patients with an intraabdominal tumor (Burkitt's) or those who are immunocompromised. In one report serum uric acid declined and urinary volume increased over 2 days treatment with PD [24].

Hemofiltration (CAVH, CVVH) offers a gradual, yet continuous method for removal of cellular byproducts and fluid. CAVH has recently been used in the treatment of tumor lysis syndrome [25, 26]. Heney et al. [26] reported successful reduction of uric acid and phosphorus in an 8-year-old boy with an abdominal tumor who developed hyperuricemia and hyperphosphatemia postoperatively, without significant oliguria or azotemia. Anticipating complications from chemotherapy, they initiated CAVHD, and in 2 days were able to lower the plasma uric acid from 0.9 mmol/l to less than 0.4 mmol/l and to lower the plasma phosphate from 3.3 to less than 1.0 mmol/l. Uric acid clearance in the ultrafiltrate was 6.2 ml/min per 1.73 m^2 as was phosphate clearance. Urinary uric acid clearance was not reported, however the urinary clearance of phosphate was 2.0 ml/min per 1.73 m^2, less than that of CAVH clearance. CVVHD has been used to treat two patients with Burkitt's lymphoma and acute renal failure due to tumor lysis syndrome [25]. In one patient, CVVH was initiated the day prior to initiation of chemotherapy after she did not respond to forced fluids with diuresis. Dialysis was added 2 days later when her serum phosphate and uric acid levels continued to climb [25]. Within 2 days of CVVHD, her urinary flow rate increased and CVVHD was discontinued. CVVHD was used in conjunction with hemodialysis in a 17-year-old with Burkitt's lymphoma and acute renal failure secondary to tumor lysis syndrome. Unfortunately, one cannot draw conclusions as to the efficacy of CVVHD from this patient due to its combination with hemodialysis and the short duration (11 h) of the procedure. Clearances of uric acid and phosphate were not reported.

Table 3. Comparative clearances of uric acid and phosphorus

Method	Uric acid		Phosphorus		Reference
	clearance (ml/min)	removal (g/day)	clearance (ml/min)	removal (mg/min)	
Peritoneal	15	3.4–4.8	–	–	[3, 21]
Hemodialysis	70–145	1.5–13.4	92	9.3	[3, 27]
CAVH	6.2	–	6.2	–	[27]
CVVH	–	–	–	1.0	[27]
CAVHD	–	–	–	–	–
Renal	17.1[a]	2.05[b]	10–80	–	[11]

CAVH, Continuous arteriovenous hemofiltration; CVVH, continuous venovenous hemofiltration; CAVHD, continuous arteriovenous hemofiltration

[a] ml/min per 1.73 m^2
[b] mg/min per 1.73 m^2

CVVH was used to maintain normal serum phosphorus levels in a patient with acute renal failure secondary to hyperphosphatemia after initial normalization of the phosphorus with hemodialysis [27]. The phosphate removal rate while on CVVH was 1.0 mg/min and phosphate clearance was 92 ml/min with hemodialysis. The 24-h phosphorus removal for CVVH was 1,440 mg, while phosphorus removal during a 3-h of hemodialysis was 1,670 mg, making daily CVVH almost as effective as a single dialysis treatment.

Prevention of tumor lysis using CVVH was recently reported in abstract form [28]. Five patients with Burkitt's lymphoma were prospectively begun on CVVH prior to initiation of chemotherapy. Of the five patients, only one had clinically significant changes in renal function attributable to tumor lysis syndrome, and dialysis was not required. The length of treatment ranged from 70 to 90 h, during which time most of the patients developed hypokalemia. The authors concluded that CVVH prevented renal failure in 80% of their patients. However, one should approach such a conclusion with caution, because this is a small group of children and the percentage of Burkitt's lymphoma patients requiring dialysis from the Stapleton et al. [2] paper was 25%, and probably not different from that reported for CVVH treatment. In addition, the initiation of CVVH is a complicated, expensive, and tedious undertaking not without risk of hypovolemia or reduced renal perfusion.

Urate clearance. Clearances of uric acid and phosphorus for the various dialysis methods are listed in Table 3. Uric acid clearance with hemodialysis is 80 ml/min at a blood flow of 200 ml/min and dialysate flow of 500 ml/min [23], which would achieve a clearance of 7–8 g of uric acid/24 h. Peritoneal uric acid clearance is reported to be 10–20 ml/min with removal of approximately 4 g in 24 h [24]. Using hourly passes of unknown volume, uric acid clearance was 7.9 g/24 h and 7.8 g/24 h when the serum uric acid levels were 84 mg/dl and 57 mg/dl, respectively. However, uric acid clearance during the 3rd day decreased to 3.3 g when the uric acid levels fell to 28 mg/dl, indicating a relationship between clearance and plasma uric acid level [24]. This supports simple diffusion as the means of peritoneal uric acid transport. Binding of urate to protein, which may vary between 0% and 25%, could also interfere with peritoneal transfer. The addition of 5% albumin to dialysate improved uric acid clearance [24]. The pH of many PD solutions is 5.5 or less; transperitoneal transport rates may be increased by raising the pH of the dialysate to physiological levels. The pH of commercially available dialysis solutions may be increased to 7.35 by addition of 22 mEq/l of sodium bicarbonate [24].

Phosphate clearance. Although precise clearance studies are not available in children with tumor lysis, phosphorus is not efficiently cleared by any of the dialysis modalities. Approximately 0.5–0.8 g of phosphate are removed by a single hemodialysis treatment, while 0.3–0.4 g/day are removed by continuous ambulatory peritoneal dialysis in adult males. Phosphate clearance by CAVH was reported to be 6.2 ml/min per 1.73 m^2 or equivalent to the urea clearance in the patient reported by Heney et al. [26].

Modification of drug dosing. Timing of chemotherapy around dialysis treatments may be warranted if cyclophosphamide is used, because it is cleared by hemodialysis. One might argue that active metabolites are protein bound and not likely to be removed, however administration of chemotherapy immediately following hemodialysis seems judicious, as proposed by Stapleton et al. [2]. In addition, allopurinol dosing should be adjusted during renal failure and following hemodialysis since approximately 40% may be removed [29].

In summary, tumor lysis syndrome presents a challenge to physicians caring for children with lymphoproliferative malignancies. Newer therapies such as uricase may markedly simplify the management of many of these patients. In addition, attention to phosphorus excretion and avoiding procedures that enhance phosphate precipitation may also prevent acute renal failure in patients with high tumor burden. Despite concerted efforts to address these metabolic alterations, some patients may require dialysis given the serious risk for cardiac arrythmias and sudden death from hyperkalemia and hypocalcemia. In these patients, CAVH or CVVH with dialysis offers a viable alternative to standard hemodialysis. More studies are needed to ascertain relative solute clearances and complications associated with the three available dialytic therapies.

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Literature abstract

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The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16

The European Polycystic Kidney Disease Consortium

Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disorder that frequently results in renal failure due to progressive cyst development. The major locus, PKD1, maps to 16p13.3. We identified a chromosome translocation associated with ADPKD that disrupts a gene (PBP) encoding a 14 kb transcript in the PKD1 candidate region. Further mutations of the PBP gene were found in PKD1 patients, two deletions (one a de novo event) and a splicing defect, confirming that PBP is the PKD1 gene. This gene is located adjacent to the TSC2 locus in a genomic region that is reiterated more proximally on 16p. The duplicate area encodes three transcripts substantially homologous to the PKD1 transcript. Partial sequence analysis of the PKD1 transcript shows that it encodes a novel protein whose function is at present unknown.