Chapter 4: Tumor Lysis Syndrome

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INTRODUCTION

Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities resulting from either spontaneous or chemotherapy-induced tumor cell death. Tumor cytotoxicity releases intracellular contents, including nucleic acids, proteins, and electrolytes into the systemic circulation and may lead to development of hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia. Clinically, this results in multiorgan effects such as AKI, cardiac arrhythmias, and seizures (1,2). TLS is the most common oncologic emergency (3), and without prompt recognition and early therapeutic intervention, morbidity and mortality is high.

DEFINITION

Hande and Garrow (4) first initiated a definition of the clinical and pathologic characteristics of patients at risk for developing TLS. Based on a retrospective analysis of 102 patients with non-Hodgkin lymphoma (NHL), they classified TLS as laboratory TLS (LTLS) or clinical TLS (CTLS). Cairo and Bishop (1) modified these criteria to formulate a commonly used classification system for TLS. This system (Table 1) defines LTLS when two or more of the following abnormalities are met within 3 days before or 7 days after the initiation of chemotherapy: 1) 25% decrease from baseline in serum calcium, and/or 2) 25% increase from baseline in the serum values of uric acid, potassium, or phosphorous.

The Cairo and Bishop definition assumes adequate volume expansion and prophylaxis with a hypouricemic agent. LTLS is defined as CTLS (Table 1) when LTLS is accompanied by one or more clinical manifestations such as cardiac arrhythmia, death, seizure, or AKI with an elevated serum creatinine >1.5 times upper limit of normal. Additionally, this definition of CTLS assumes that the clinical manifestations are not caused directly by the therapeutic agent. Last, a third class specifies patients with normal laboratory and clinical parameters as having no LTLS or CTLS.

Cairo and Bishop also proposed a grading system combining the definitions of no TLS, LTLS, and CTLS, with the maximal clinical manifestations in each affected organ defining the grade of TLS (1). Although this grading system attempts to provide uniform definitions to TLS severity, it is not widely used in clinical practice.

The Cairo-Bishop classification is not immune to critique despite its common use. Specifically, patients with TLS may not always have two or more abnormalities present at once, but one metabolic derangement may precede another (2). Furthermore, a 25% change from baseline may not always be significant if it does not result in a value outside the normal range (2). From a renal standpoint, Wilson and Berns (5) have noted that defining AKI on the basis of a creatinine value >1.5 times the upper limit of normal does not clearly distinguish CKD from AKI. Thus, they propose using established definitions of AKI in CTLS such as an absolute 0.3 mg/dL increase or relative 50% increase in creatinine over baseline. Finally, they point out that the Cairo-Bishop classifications cannot be applied to spontaneous TLS, which is common with high-risk malignancies, as chemotherapy is a required criterion for LTLS and CTLS.

EPIDEMIOLOGY AND RISK FACTORS

TLS is most commonly described in NHL, particularly Burkitt-type lymphoma (BTL), as well as other hematologic malignancies, such as acute lymphocytic and lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (6–8), and less commonly in chronic

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leukemias (9–11) and multiple myeloma (12,13). More rarely, TLS has also been described with solid malignancies (14,15) with particular features, including large tumor burden, metastatic disease, specifically in the liver, short doubling time, increased chemosensitivity, and elevated uric acid and lactate dehydrogenase (LDH) (15). Among solid tumors, small-cell carcinoma of the lung, germ cell tumors, neuroblastoma, and breast carcinoma have all been linked to development of TLS (8). TLS is usually associated with cytotoxic chemotherapy but reports have also linked it to the use of imatinib (11), bortezomib (12), corticosteroids (16,17), rituximab (18), methotrexate (19), and thalidomide (13,20). There are also case reports of TLS following total body irradiation (21) and chemoembolization (22). Last, TLS may also be spontaneous, i.e., not requiring initiation of cytotoxic therapy. This has been most frequently described in BTL (23–25).

The incidence of TLS varies based on the underlying malignancy and the definition of TLS. Most incidence data are from older, retrospective studies that precede the Cairo-Bishop classification, so there is considerable heterogeneity in the data. In a review of 102 patients with high-grade NHL and using the Hande-Garrow classification, LTLS was seen in 42% of patients, with CTLS occurring only in 6% (4). In BTL, however, 56% and 11% of patients met criteria for LTLS and CTLS, respectively. Mato et al. (26) studied 194 patients receiving induction therapy for AML and found a TLS incidence of 9.8%. In a mixed adult and pediatric study of 788 European patients with acute leukemia or NHL (27), the overall incidence of LTLS and CTLS was 18.9% and 5%, respectively. When classified by tumor type, LTLS and CTLS incidence rates of 14.7% and 3.4% were seen in AML patients, respectively; 21.4% and 5.2% in ALL patients, respectively; and 19.6% and 6.1% in patients with NHL, respectively (27). Wössman et al. (28) reviewed the incidence and complications of 1,791 children with NHL and reported an overall incidence of 4.4%, of which 26% had B-cell ALL (B-ALL).

**Pathophysiology and Clinical Manifestations**

TLS is a direct consequence of cell lysis and release of intracellular products. When clearance of these products, by excretion (renal or hepatic excretion or phagocytosis by the reticuloendothelial system) (23), is impaired and their serum burden increases, the clinical sequelae of TLS may occur. Of these cellular products, nucleic acids (converted to uric acid), potassium, and phosphorus are particularly important in the pathophysiology of TLS.

**Hyperuricemia**
The nucleic acids adenine and guanine are metabolized to xanthine, which is further metabolized by xanthine oxidase to the water-insoluble uric acid (5) (Figure 1). Because humans lack a functional gene for urate oxidase (uricase), which further metabolizes uric acid to the freely soluble and excretable allantoin, patients with high-risk malignancy are susceptible to rapid increases in serum uric acid. Uric acid is freely filtered at the glomerulus, and handling in the renal proximal tubule

<table>
<thead>
<tr>
<th>Metabolite or electrolyte</th>
<th>Criterion for diagnosis</th>
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<tbody>
<tr>
<td>Uric acid</td>
<td>≥8 mg/dL or 25% increase from baseline</td>
</tr>
<tr>
<td>Potassium</td>
<td>≥6 mEq/L or 25% increase from baseline</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>≥6.5 mg/dl (children), ≥4.5 mg/dl (adults), or 25% increase from baseline</td>
</tr>
<tr>
<td>Calcium</td>
<td>≥25% decrease from baseline</td>
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</table>

**Clinical Tumor Lysis Syndrome**

- LTLS and one or more of the following: 1) creatinine × ≥1.5 ULN (age >12 years of age or age adjusted); 2) cardiac arrhythmia or sudden death; 3) seizure

**Table 1. Cairo-Bishop definition of laboratory tumor lysis syndrome and clinical tumor lysis syndrome**

<table>
<thead>
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**Note:** LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal.
is a combination of reabsorption and secretion via the luminal urate/anion exchanger urate transporter 1 (URAT-1) and the basolateral organic anion transporter (OAT) (34). URAT-1 is an apical membrane transporter and exchanges anions for urate absorption from the tubular lumen. It is critical in regulating urate levels and is targeted by uricosuric and antiuricosuric agents (34). When the capacity to transport luminal uric acid is overwhelmed, there is potential for uric acid to crystallize within the tubular lumen. An acidic urine pH favors this process.

Uric acid crystals can cause direct tubular injury by obstruction, but other pathways for injury include induction of chemokine-mediated inflammation from monocyte chemotactrant protein-1 (MCP-1) (35) and macrophage migration inhibition factor (MIF) (36). There are also crystal-independent mechanisms which target hemodynamics. These include increased peritubular capillary pressures, increased vasoconstriction, and decreased blood flow (5,37–39). Uric acid may also prevent recovery from AKI in TLS, as it has been shown to inhibit proximal tubule cell proliferation (38). These diverse mechanisms are united in their propensity to cause AKI. Clinically, hyperuricemia is unlikely to cause symptoms because urinary crystallization of uric acid does not result in the renal colic, which is typical of uric acid nephrolithiasis.

**Hyperkalemia**

Massive tumor cell lysis releases potassium into the extracellular environment, leading to severe hyperkalemia when uptake capacity by muscle and liver is exceeded, especially in

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Risk</th>
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<tbody>
<tr>
<td>Solid tumor</td>
<td>Low</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Low</td>
</tr>
<tr>
<td>Chronic leukemia</td>
<td>Low</td>
</tr>
<tr>
<td>Lymphoma: Burkitt type</td>
<td>CML: low</td>
</tr>
<tr>
<td></td>
<td>CLL w/alkylating agents: low</td>
</tr>
<tr>
<td></td>
<td>CLL w/targeted or biological agents: intermediate</td>
</tr>
<tr>
<td></td>
<td>Early stage and LDH &lt;2 × ULN: intermediate</td>
</tr>
<tr>
<td></td>
<td>Early stage and LDH &gt;2 × ULN: high</td>
</tr>
<tr>
<td></td>
<td>Advanced stage: high</td>
</tr>
<tr>
<td>Lymphoma: non-Burkitt type</td>
<td>Child with stage III/IV disease: intermediate</td>
</tr>
<tr>
<td></td>
<td>All others: low</td>
</tr>
<tr>
<td>Anaplastic large cell</td>
<td>Early stage and LDH &lt;2 × ULN: intermediate</td>
</tr>
<tr>
<td></td>
<td>Early stage and LDH &gt;2 × ULN: high</td>
</tr>
<tr>
<td></td>
<td>Advanced stage: high</td>
</tr>
<tr>
<td>Hodgkin, small lymphocytic, follicular, marginal zone B cell, MALT, nonblastoid mantle cell, cutaneous T cell</td>
<td>Adult with normal LDH: low</td>
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<tr>
<td></td>
<td>Child with stage II/II disease: low</td>
</tr>
<tr>
<td></td>
<td>Adult with LDH &gt; ULN and nonbulky disease: intermediate</td>
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<tr>
<td></td>
<td>Adult with LDH &gt; ULN and bulky disease: high</td>
</tr>
<tr>
<td></td>
<td>Child with stage III/IV disease and LDH &lt;2 × ULN: intermediate</td>
</tr>
<tr>
<td></td>
<td>Child with stage III/IV disease and LDH &gt;2 × ULN: high</td>
</tr>
<tr>
<td>Adult T-cell lymphoma, diffuse large B cell, peripheral T cell, transformed, or blastoid mantle cell</td>
<td>Leukemia: Burkitt type</td>
</tr>
<tr>
<td></td>
<td>Acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td></td>
<td>Acute lymphoblastic leukemia (ALL)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Risk</td>
</tr>
<tr>
<td>Absent</td>
<td>If low risk disease, no change</td>
</tr>
<tr>
<td></td>
<td>If intermediate risk disease and normal UA, phosphorus, and potassium, no change</td>
</tr>
<tr>
<td></td>
<td>If UA, phosphorus, or potassium &gt; ULN, intermediate risk disease becomes high risk</td>
</tr>
<tr>
<td>Present</td>
<td>Low risk disease become intermediate risk</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk disease becomes high risk</td>
</tr>
</tbody>
</table>

CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase; AML, acute myeloid leukemia; WBC, white blood cell count; ALL, acute lymphocytic and lymphoblastic leukemia; UA, urinalysis; ULN, upper limit of normal.
the setting of CKD or AKI. Muscle weakness may be the initial symptom, but cardiac arrhythmia, manifested initially by peaked T-waves, widened QRS complexes, and sine waves, is the feared complication.

Hyperphosphatemia and hypocalcemia
Because phosphate is an intracellular electrolyte, cell lysis releases significant amounts of it. However, malignant hematologic cells may contain four times more intracellular phosphate in comparison to normal mature lymphoid cells (3), making hyperphosphatemia a particular issue with tumor cell lysis. Because phosphorus excretion is tied to kidney function, hyperphosphatemia occurs when the kidney’s excretory capacity is overwhelmed. Thus, preexisting CKD or AKI enhances risk for hyperphosphatemia with TLS. Spontaneous tumor lysis, however, is less commonly associated with hyperphosphatemia and may be due to rapid uptake of extracellular phosphate by residual highly metabolically active tumor cells (5). Hyperphosphatemia may cause nausea, vomiting, diarrhea, or lethargy, but it exerts its predominant toxicity by binding to calcium cations. This results in secondary hypocalcemia and its downstream neuromuscular and cardiovascular effects such as cramps, hypertension, tetany, and arrhythmias. Additionally, calcium–phosphate precipitates may deposit in tissues, as seen in nephrocalcinosis, including the renal interstitium.

AKI
AKI in TLS may be either due to the aforementioned effects of acute urate nephropathy or hyperphosphatemic nephrocalcinosis affecting the renal tubulointerstitium or a combination of the two. Some studies have suggested that a urine uric acid to creatinine ratio of >1 may be specific to uric acid nephropathy (40), but another study has noted high uric acid to creatinine ratios in AKI from other etiologies (41).

The association between AKI and TLS has been demonstrated across various populations and tumor subtypes (5). Annemans et al. (27) found that in patients with leukemia and NHL who had TLS, 45% had AKI. A smaller pediatric cohort of B-cell NHL or ALL noted renal insufficiency in 20% percent of the study population (42). Although the data were not broken down into cause of AKI, the incidence of TLS was similar at 17%, suggesting that AKI and TLS were also linked in this population. AKI due to TLS may be asymptomatic or include symptoms of uremia, including nausea, vomiting, and lethargy.

MANAGEMENT
Prophylaxis and monitoring
Prevention of TLS begins with recognition of risk factors and close laboratory and clinical monitoring. Patients at highest risk of developing TLS (Table 2) require intensified monitoring with more frequent electrolyte checks. Patients with high-risk disease may be prone to lactic acidosis from massive tumor cell necrosis. Because acidosis inhibits uric acid excretion (43), prompt recognition and correct of acidosis may prevent or ameliorate uric acid nephropathy. Additionally, nonsteroidal anti-inflammatory drugs, iodinated radiocontrast dye, and other potentially nephrotoxic therapeutic agents should be avoided to abrogate the risk of AKI from TLS.

Volume expansion
Delivery of crystalloid intravenous fluids (IVFs) is recommended for all patients and is essential for those with higher TLS risk. Volume expansion supports adequate intravascular volume and renal blood flow, which maintain glomerular filtration. This is the cornerstone of uric acid, potassium, and phosphate excretion and may delay and prevent the need for renal replacement measures (2,6,44). High-dose IVFs up to 3 L have been recommended (2), for a target urine output of ≥2 mL/kg/h. Diuretics may be necessary if patients develop volume overload, but routine use is not recommended to avoid volume depletion.

Urinary alkalinization
Alkalization makes physiologic sense, as increasing urine pH from 5 to 7 can increase the solubility of uric acid >10-fold (28). However, urinary alkalization decreases calcium-phosphate solubility (2), thereby exacerbating its precipitation
and deposition. Furthermore, if urinary alkalinization results in rising serum pH, free calcium may bind albumin more avidly and further exacerbate hypocalcemia (45). Thus, urinary alkalinization is not recommended in the management of TLS (2,6,45).

**Allopurinol**

Allopurinol is converted in vivo to oxypurinol and as a xanthine analog acts as a competitive inhibitor of xanthine oxidase and blocks the conversion of purines to uric acid (6,46) (Figure 1). This prevents hyperuricemia but does not treat preexisting hyperuricemia (6). Furthermore, because oxypurinol also inhibits the conversion of xanthine to uric acid, serum and urine xanthine levels may rise and precipitate xanthine crystal deposition in the renal tubules and xanthine-induced obstructive nephropathy (47). Administration of allopurinol is recommended for prophylaxis in patients with low and intermediate risk of developing TLS (2,6). Smalley et al. (48) studied 1,172 patients to evaluate the efficacy and safety of intravenous allopurinol in patients with hyperuricemia. They noted reduced uric acid levels in 57% of adults and 88% of children. When used as prophylactic therapy, allopurinol prevented an increase in uric acid levels in 93% of adults and 92% of children.

Because oxypurinol excretion is by the kidney, dose adjustments are necessary for patients with CKD and AKI. Allopurinol has been associated with a hypersensitivity syndrome with rash, acute hepatitis, and eosinophilia (45,49). Allopurinol reduces the clearance of purine-based chemotherapeutic agents such as 6-mercaptopurine and azathioprine (6). It may also interact with azathioprine and cyclophosphamide in potentiating severe bone marrow suppression (6,45).

**Febuxostat**

Febuxostat is a novel xanthine oxidase inhibitor lacking the hypersensitivity profile of allopurinol. Because it is metabolized to inactive metabolites by the liver, adjustment for reduced GFR is not necessary. It has been proposed as a viable alternative to allopurinol in TLS prophylaxis for patients with allopurinol hypersensitivity or renal dysfunction (45). A recently completed phase III study of febuxostat versus allopurinol in TLS prevention found significantly lower serum uric acid in the febuxostat but found no significant difference in serum creatinine change compared with allopurinol (50). Febuxostat use has been limited by its significant cost compared with generically available allopurinol (45).

**Rasburicase**

Rasburicase (Elitek) is an *Aspergillus*-derived recombinant urate oxidase approved by the US Food and Drug Administration (FDA) in 2002 for the initial management of hyperuricemia in pediatric patients with leukemia, lymphoma, and solid tumor malignancies receiving anticancer therapy (51). It was subsequently approved for use in adults in 2009 (51). Rasburicase catalyzes the conversion of uric acid to allantoin, carbon dioxide, and hydrogen peroxide (Figure 1). Allantoin is 5- to 10-fold more soluble than uric acid (52) and is readily excreted. Prior to FDA approval, 1,069 adult and pediatric patients received rasburicase on a compassionate use basis (53). Decreased serum uric acid levels were observed in 99% of children and 100% of adults. Hemodialysis was performed in only 2.8% of patients. In a study of 131 patients with newly diagnosed leukemia or lymphoma, Pui et al. (54) reported a decrease in plasma uric acid concentrations from 9.7 to 1 mg/dL (P = 0.0001) in 65 patients who presented with hyperuricemia and a decrease from 4.3 to 0.5 mg/dL (P = 0.0001) in the remaining patients. There was negligible toxicity, and no patients required dialysis.

Cortes et al. (55) compared response rates in dosing rasburicase alone versus rasburicase followed by allopurinol versus allopurinol alone. They reported a plasma uric acid response rate of 87% in the rasburicase group, 78% in the rasburicase followed by allopurinol group, and 66% in the allopurinol group, with a significantly greater response for rasburicase compared with allopurinol in the overall study population (P = 0.001), in patients at high risk for TLS (89% versus 68%; P = 0.012), and in those with baseline hyperuricemia (90% versus 53%; P = 0.015). Of note, there are no prospective studies to date that have examined the impact of rasburicase on relevant clinical end points such as morbidity from AKI. Nonetheless, rasburicase should be used for prophylaxis in patients with high risk of developing TLS (7). The FDA-approved dosing guidelines recommend 0.2 mg/kg in 50 mL normal saline as a 30-minute intravenous infusion once daily for up to 5 days (51). Length of treatment is related to control of plasma uric acid levels, but use of rasburicase for >5 days is rarely needed (6,51). In comparison with generically available allopurinol, rasburicase is significantly more expensive (up to $3,600 per 7.5-mg vial) (45), and in most published studies, one-time dosing was sufficient to suppress hyperuricemia.

Rasburicase does not require dosing adjustment for GFR and is not known to have any known clinically relevant drug–drug interactions (51,56). Adverse reactions are rare but may include rash, increased liver enzyme levels, headaches, fever, vomiting, and nausea (56).

Rasburicase is active ex vivo, so blood samples for serum uric acid levels must be stored on ice to avoid erroneously low results (45). Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency can develop significant methemoglobinemia and hemolysis due to oxidative stress triggered by hydrogen peroxide (57,58). Accordingly, patients should have G6PD status tested prior to starting rasburicase.

**RRT**

The need for renal replacement has significantly reduced since the advent of rasburicase, but about 1.5% of children and 5% of adults require dialysis during induction therapies (53). Indications for RRT are similar to those for AKI from other causes, but due to the rapid onset of the clinical manifestations of TLS, the threshold for initiating dialytic therapies is lower than in other situations. Although intermittent hemodialysis (IHD) may be sufficient for most patients, continuous RRT (CRRT) at high dialysate or replacement fluid flow rates (>3-4 L/h) may be necessary in those patients with severe TLS who...
experience rebound in serum potassium and phosphorous levels with IHD (45, 59, 60).

PROGNOSIS

There are many confounding factors that impact clinical outcomes in patients with malignancies, particularly in those who have TLS, but AKI appears to be a significant predictor of short- and long-term mortality from TLS. A study comparing hematologic cancer patients without AKI to patients with AKI (61) showed significantly lower hospital mortality (7% and 21%, respectively) and 6-month mortality (51% and 66%, respectively) in patients without AKI. TLS is most common during initial presentation of disease because relapsed malignancies are significantly more chemoresistant (5). There are fewer case reports of TLS in recurrent disease (62).

CONCLUSIONS

TLS is a common oncolgic emergency that requires immediate diagnosis and prompt treatment to avoid morbidity and mortality. Understanding the diagnostic criteria for TLS, knowing the tumor types at high risk for TLS, and instituting prophylactic and treatment measures are essential for the nephrologist who treats patients with malignant diseases.

TAKE HOME POINTS

- TLS is the most common oncolgic emergency.
- The risk of TLS depends on tumor type but is also influenced by other factors.
- There is a high burden of AKI in patients with TLS.
- Prophylaxis with volume expansion is the mainstay of preventing TLS in any patient-risk category.
- Patients at high risk for TLS should receive rasburicase for initial treatment of hyperuricemia.

ACKNOWLEDGMENTS

Dr. Edeani’s work is supported by the intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

REFERENCES

**REVIEW QUESTIONS**

1. Which of the following cancers are considered high risk for tumor lysis syndrome?
   a. Lung cancer
   b. Lung cancer and patient has AKI
   c. Burkitt-type lymphoma, advanced stage
   d. Adult T-cell lymphoma and normal LDH
   e. ALL with WBC $<100 \times 10^9/L$ and LDH $<2 \times$ ULN

   Answer: c is correct. As shown in Table 2, the risk of TLS depends on type of malignancy, stage or extent of disease, and presence/absence of renal disease. Burkitt-type lymphoma that is in an advanced stage confers a high risk of TLS. Solid tumors such as lung cancer are considered low risk, and the presence of renal failure raises that to intermediate risk. Thus, answers a and b are incorrect. Adult T-cell lymphoma is considered low risk if LDH is normal and acute lymphoblastic leukemia with WBC $<100 \times 10^9/L$ is considered intermediate risk if LDH $<2 \times$ ULN.

2. Which of the following electrolyte abnormalities define laboratory TLS?
   a. Hypokalemia
   b. Hypercalcemia
   c. Hypophosphatemia
   d. Hypernatremia
   e. Hypocalcemia

   Answer: e is correct. As show in Table 2, laboratory TLS is defined by two or more abnormalities in serum electrolytes. These include a 25% increase from baseline in phosphorous, potassium, or uric acid or a 25% decrease from baseline in calcium. Thus, answers a, b, and c are incorrect. Serum sodium concentration is not directly affected in TLS; therefore, answer d is incorrect.

3. Rasburicase is part of the treatment regimen for tumor lysis syndrome because
   a. It increases urinary alkalinization
   b. It improves the ability of proximal tubular cells to recover from AKI
   c. It stimulates the URAT1 transporter to increase uptake of uric acid from the tubular lumen
   d. It catalyzes the conversion of uric acid into allantoin
   e. It prevents xanthine crystal deposition in tubular lumens

   Answer: d is correct. Rasburicase, as shown in Figure 3, is recombinant urate oxidase that enzymatically transforms uric acid into allantoin. It has no known effect on urine pH, renal tubular cells, URAT1 transporters, or xanthine crystals. Thus, answers a–c and e are incorrect.