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## Acute tumor lysis syndrome: a comprehensive review

*Síndrome de lise tumoral: uma revisão abrangente da literatura*

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Received from Saint-Louis University Hospital, Medical Intensive Care Unit, Paris, France

Submitted on March 30, 2008

Accepted on July 10, 2008

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### ABSTRACT

Tumor lysis syndrome is characterized by the massive destruction of malignant cells and the release in the extracellular space of their content. While Tumor lysis syndrome may occur spontaneously before treatment, it usually develops shortly after the initiation of cytotoxic chemotherapy. These metabolites can overwhelm the homeostatic mechanisms with development of hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia. These biological manifestations may lead to clinical manifestations including, acute kidney injury, seizure, or sudden death that require intensive care. Since clinical tumor lysis syndrome is associated with a poor prognosis both prevention of tumor lysis syndrome and prevention of clinical consequences of tumor lysis syndrome are mandatory. The objective of this review is to describe pathophysiological mechanisms, biological and clinical manifestations of tumor lysis syndrome and to provide up-to-date guidelines to ensure prevention of tumor lysis syndrome. Review of selected studies on tumor lysis syndrome pub-

lished at the PubMed database (www.pubmed.gov) during the last 20 years. Additional references were retrieved from the studies initially selected. Tumor lysis syndrome is a frequent and a life-threatening complication of the newly diagnosed malignancies. Preventive measures, including hydration, uricolytic agents, eviction of factors predisposing to acute kidney injury and, in the more severe patients, on prophylactic renal replacement therapy, are required in way to prevent or limit clinical consequences of tumor lysis syndrome. However optimal timing and modalities of prevention remains unknown and may be modified by the changing spectrum of patients at risk of tumor lysis syndrome. Development and validation of risk based strategies is required in way to limit the high morbidity and mortality of this complication.

**Keywords:** Tumor Lysis syndrome; Antineoplastic agents/\*adverse effects Hyperphosphataemia; Hypercalcemia; Hyperuricemia; Renal insufficiency, acute; Leukemia; Lymphoma, non-Hodgkin; Intensive care units; Kidney diseases/chemically induced; Uric acid/adverse effects

### INTRODUCTION

Acute kidney injury is a frequent complication associated with high morbidity and mortality in critically ill cancer patients.<sup>1-6</sup> Multiple etiologies of acute kidney injury are frequently associated, sepsis and hypoperfusion being the commonest.<sup>4,6</sup> However, several factors specifically associated with the underlying malignancy may be expected.<sup>4,6</sup>

Tumor lysis syndrome (TLS) is a dreadful complication that may occur spontaneously or as consequences of cancer chemotherapy initiation.<sup>7-8</sup> This

syndrome is characterized by the massive destruction of malignant cells and the release in the extra-cellular space of their content.<sup>7-8</sup> Therefore, TLS may lead to the development of an acute kidney injury which may, in itself, cause substantial morbidity and mortality.<sup>9</sup> The association between TLS and acute kidney injury may increase dramatically kaliemia and phosphataemia leading potentially to cardiac arrhythmia or sudden death.<sup>7-8</sup>

The objective of this review is to describe clinical and biological consequences of TLS, pathophysiological mechanisms leading to this syndrome and to provide up-to-date guidelines to ensure prevention and prompt management of TLS.

Combinations of key words related to acute kidney injury (e.g.: acute kidney injury, acute renal failure, dialysis, hemofiltration, ICU), cancer (cancer, malignancy, chemotherapy, bone marrow transplantation), and tumor lysis syndrome (acute tumor lysis syndrome, tumor lysis syndrome, "Tumor Lysis Syndrome" [MeSH], hyperuricaemia, hyperphosphataemia, urates nephropathy, nephrocalcinosis [MeSH]) were used to search the MedLine database, OVID database and the Cochrane Group database. The last search was performed in June 2008. We checked the bibliographies of retrieved reports and reviews. We carefully checked the reviews and articles focusing on acute kidney failure in the general ICU population and the articles focusing on the critically ill cancer patients.

Most relevant articles were selected by the authors in way to give a concise and an up-to-date overview of the problem. However, it must be noted that only few clinical or experimental studies have been performed in this field. As consequences, the level of evidence for most of the conclusion of this article (except for the rasburicase use) would have been quoted as 2- to 4 [Case-control or cohort studies with a high risk of confounding factors, case series and expert opinion].

## DEFINITION

While the metabolic abnormalities associated with tumor lysis syndrome are generally agreed upon, there is currently no consensus on definition or grading system. The first developed classification was those of Hande and Garrow in 1993. Cairo and Bishop recently modified this definition (Chart 1).<sup>7</sup> Accordingly to this definition, metabolic derangement (hyperkalaemia, hyperphosphataemia, hyperuricaemia and hyperkalaemia) allows diagnosis of biological TLS while clinical manifestations (cardiac, renal or neurological manifestations of TLS) in the setting of biological TLS lead to the diagnosis of clinical TLS. Al-

though this definition is a helpful tool allowing diagnosis and classification of TLS none of the biological manifestations of TLS is specific. For example, acute kidney injury may mimic every of the biological manifestations of TLS. Distinction between TLS complicated of AKI from AKI without TLS may therefore be challenging.

**Chart 1 – Definitions of biological and clinical tumor lysis syndrome accordingly to Cairo and Bishop<sup>7</sup>**

Biological TLS: at least two of the following	
Calcaemia (non ionized)	< 1.75 mmol/L or -25% from baseline
Kaliemia	6 mmol/L or +25% from baseline
Urates	476 µmol/L or +25% from baseline
Phosphates	1.45 mmol/L or +25% from baseline
Clinical TLS: defined as a biological TLS (above) plus one of the following	
Renal manifestation	Acute kidney injury
Cardiovascular manifestation	Cardiac arrhythmia or sudden death
Neurological manifestation	Seizure

TLS – Tumor lysis syndrome

## INCIDENCE AND RISK STRATIFICATION

Early recognition of patients at high risk for TLS, or at high risk of acute kidney injury during TLS may allows a risk based strategy aiming to avoid development of an acute kidney injury. This syndrome typically occurs in patients with high-grade hematological malignancies (i.e. high grade non-Hodgkin's lymphoma, acute myeloid and acute lymphoid leukemia).<sup>10-15</sup> Indeed, despite urate oxydase, 10% to 50% of patients with high-grade malignancies may develop TLS.<sup>16-19</sup> Up to one third of these patients will develop an acute kidney injury, a condition associated with a poor prognosis.<sup>17-19</sup> Classical risk factors of TLS include large tumor burden, lactate dehydrogenase levels above 1500 IU, extensive bone marrow involvement, and high tumor sensitivity to chemotherapeutic agents.<sup>11</sup> TLS has also been reported in patients with fast-growing solid tumors such as testicular cancer.<sup>20-21</sup> Additionally, several low grade hematological malignancies including chronic lymphoid lymphoma, solid tumors or myeloma have recently been described to be associated with TLS (Chart 2).<sup>22-26</sup> This may be due to

the increasing efficiency of novel anticancer therapies such as rituximab, bortezomib, thalidomide, tamoxifen or interferon  $\alpha$ .<sup>24-29</sup>

Last, spontaneous TLS may be more frequent than usually supposed. Indeed, recent studies report that up to one-third of TLS may appear before initiation of chemotherapy.<sup>18,30</sup>

**Chart 2 – Malignancies with low tumor lysis syndrome rate and malignancies recently associated with tls in case report or case series**

Malignancies with low risk of TLS

Medulloblastoma<sup>42</sup>

Breast carcinoma<sup>20</sup>

Gastrointestinal carcinoma<sup>20</sup>

Recent Anecdotal Reports

Rhabdomyosarcoma<sup>20</sup>

Vulvar carcinoma<sup>20</sup>

Ovarian carcinoma<sup>20</sup>

Thymoma<sup>21</sup>

Soft tissue sarcomas<sup>20</sup>

Metastatic seminoma<sup>21</sup>

Melanoma<sup>29</sup>

Prostatic neoplasm<sup>46</sup>

Hepatoblastoma<sup>20</sup>

Hepatocarcinoma<sup>27,47</sup>

Colonic carcinoma<sup>47</sup>

Pheochromocytoma<sup>47</sup>

TLS – Tumor lysis syndrome

**PATHOPHYSIOLOGY AND CLINICAL PRESENTATION**

Tumor lysis syndrome results from massive destruction of malignant cells. While TLS may occur spontaneously before treatment, it however usually develops shortly after the initiation of cytotoxic chemotherapy.<sup>12</sup>

Massive cells destruction will lead to a rapid release of intracellular anions, cations and metabolic products of proteins and nucleic acids into the bloodstream.<sup>21</sup> AKI may develop, the most common mechanism being uric acid crystal formation in the renal tubules secondary to hyperuricaemia. Another cause may be calcium phosphates deposition related to hyperphosphataemia. While AKI leads to further increase in above describe metabolites, a vicious circle will therefore be initiated.

**Clinical Presentation**

Several symptoms may appear as consequences of the TLS, acute kidney injury being the commonest. Acute

kidney injury can lead to fluid overload and pulmonary edema; hyperkalaemia or hyperphosphataemia enhanced by renal failure may lead to cardiac arrhythmia or sudden death; and last, calcium and phosphates abnormalities may lead to infrequent muscle cramps or seizures.<sup>7,8,18</sup> Although acute kidney injury may develop in up to one third of patients with TLS, cardiac manifestations or neurological manifestations of TLS remains rare.<sup>18</sup>

**Biological Manifestations**

***Uric acid***

Malignant cells carry a large burden of nucleic acid products due to their high cellular activity and turnover. The release in the extra cellular space of purine nucleic acid and their subsequent transformation into uric acid will lead to hyperuricaemia.<sup>31-33</sup> Hyperuricaemia is considered to be necessary for the development of urate nephropathy since urates are poorly soluble in water and may lead to crystals deposit.<sup>34</sup> Additional factors may modify the rate of urates precipitation. Urinary pH is one of these factors, the uric acid pKa (5.4–5.7) being responsible of a further decrease in its solubility in presence of an acidic pH. In addition, the urinary flow is associated with high variations of tubular concentration of uric acid<sup>35</sup>. These two factors may therefore modify the threshold at which uric acid precipitates.<sup>35</sup>

***Hyperphosphataemia and hypocalcaemia***

Cell death releases nuclear material, including nucleotides and phosphates. Malignant cells may contain as much as fourth time the intracellular phosphorous contained in a mature lymphocyte.<sup>13</sup>

This large burden may saturate the renal capacity to excrete phosphates and may lead to precipitation of calcium-phosphates crystals, nephrocalcinosis, urinary obstruction, and tissue deposits. Hypocalcaemia may result of phosphates calcium crystals deposition and is rarely symptomatic.

Calcium phosphates crystal deposition has been reported to occur when the [non ionized Calcium] X [Phosphates] molar product exceed 4.6.<sup>36</sup> Nevertheless, the method leading to this estimation is subject to caution and this cut-off must is only be interpreted with caution. In addition, hypocalcaemia that appears as consequence of the calcium phosphates deposition will lead to an underestimation of the [non ionized Calcium] X [Phosphates] molar product.

***Hyperkalaemia***

The large burden of potassium released as consequenc-

es of the cells destruction may overwhelm the renal excretion ability and lead to a hyperkalaemia. Moreover, acute kidney injury or the tumor lysis associated-acidosis may further enhance this hyperkalaemia. In addition, an early peak in serum concentration may appear as it has been supposed that stress due to radiotherapy or chemotherapy may reduce ATP levels and results in leakage of potassium out of the tumor cells before complete lysis.<sup>21</sup>

**Acidosis**

Lactic acidosis as been retrieved in association with this syndrome and its extent is correlated with the severity of TLS.<sup>37</sup> Pathophysiological mechanisms leading to this lactic acidosis are probably multiple, including hepatic failure and tumor ischemia resulting from the poor neovascularisation of the tumors.<sup>38</sup> However, it has been recently demonstrated that lactic acidosis can be caused by the loss of mitochondrial membrane potential during apoptosis.<sup>37</sup> Therefore, massive apoptosis of a tumor mass during cancer chemotherapy may lead to a lactic acidosis and may be a pathological event of the tumor lysis syndrome.

**PREVENTION AND TREATMENT**

Three steps must be distinguished: a) prevention of TLS; b) Prevention of clinical manifestations during biological TLS; and c) prevention of further organ dysfunction in TLS with clinical manifestations. The goal of these measures remains to prevent development of

an acute kidney injury, which will enhance dramatically biological manifestations of TLS as well as its clinical consequences. Therefore, two primary end-points can be delineated: the control of hyperuricaemia and the prevention of nephrocalcinosis. These measures should include renal replacement therapy each time metabolic disturbances are not controlled within 6 hours after initiation of prevention. In addition, if acute kidney injury develops despite prevention, extra-renal therapy should be initiated quickly, aimed at clearance of uric acid and phosphates in way to limit further kidney impairment.<sup>39</sup>

In patients with very aggressive tumors, hypophosphataemia and hypokalaemia might be present before cancer chemotherapy initiation. These abnormalities give evidence of a high risk of TLS, and should therefore not be corrected. Preventive measures are summarized in the Chart 3.

**Fluid expansion**

Treatment's cornerstone remains the aggressive hydration through saline isotonic and aims to maintain a high urinary output allowing the urinary elimination of both uric acid and phosphates.<sup>7,35,39</sup> Moreover the volume expansion will decrease uric acid, phosphates and potassium serum concentrations.<sup>8</sup> If urinary output decreases despite adequate fluid intakes, diuretics have been proposed, sometime in addition with mannitol.<sup>7</sup> However, diuretics are only poorly effectives. Moreover, development of an oliguria indicates an acute kidney injury, and

**Chart 3 – Prevention and treatment of tumor lysis syndrome**

General Measures		
Avoid		
Correction of hypokalaemia or hypophosphataemia before induction		
Urine alkalization		
Correction of hypocalcaemia, unless symptomatic		
Use of diuretics		
Prevention of TLS	Prevention of cTLS	Therapy of cTLS
Volume expansion	Volume expansion	Volume expansion
Urate oxidase if right risk for TLS, alloprino- rinol otherwise	Urate oxidase	Urate oxidase
Delete phosphates, potassium and calcium from perfusion	Delete phosphates, potassium and calcium from perfusion	Delete phosphates, potassium and calcium from perfusion
	Initiate RRT after 6 hours of management if failure to normalize phosphataemia	Initiate RRT: After 6 hours if failure to normalize phosphataemia or renal function Immediately if cardiac or neurological manifestation

TLS – Tumor lysis syndrome, cTLS – Clinical Tumor lysis syndrome, RRT – renal replacement therapy

diuretics may delay the initiation of a required prophylactic renal replacement therapy. Last, innocuousness of diuretics in AKI is far to have been demonstrated.<sup>40</sup>

Although usually recommended in way to promote elimination of urates, urine alkalinization remains controversial. The availability of a fast-acting recombinant urate oxidase therapy has considerably reduced the risk of urate nephropathy.<sup>15,41</sup> In addition, urine alkalinization may induce calcium phosphates deposition.<sup>42-43</sup> And last, it has been long recognized that a high tubular fluid flow is the primary mechanism of protection in acute urate nephropathy and that urine alkalinization play minor preventive role.<sup>35</sup> Therefore, we believe that this poorly effective and potentially harmful treatment should not be recommended routinely anymore.

### Hypouricaemic agents

In addition to the hydration, several hypouricaemic agents may reduce urate levels. Non-recombinant urate oxidase (Uricozyme<sup>®</sup>), which was available in Europe, was associated with high rate of allergic reactions. More recently, recombinant urate oxidase (Rasburicase<sup>®</sup>) has been shown to reduce uric acid levels, thereby diminishing the risk of uric acid deposition nephropathy.<sup>15,41</sup> This agent transforms urate into allantoin which is far more soluble in the urine<sup>7</sup>. Recombinant urate oxydase has been shown to decrease median uric acid concentration from 577 to 60  $\mu\text{mol/L}$  within 4 hours of therapy.<sup>14</sup> Moreover, Recombinant urate oxydase has been shown to reduce significantly urates exposure time when compared to allopurinol.<sup>15</sup> Although very effective, the recombinant urate oxydase is however also very expensive and its use should be limited to the prevention of TLS in high risk patients, or treatment of established tumor lysis syndrome<sup>44</sup>. Moreover, Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.<sup>45</sup> Indeed, rasburicase breaks down uric acid and accelerates catabolism of its precursors, leading to production of hydrogen peroxide and, in patients with G6PD deficiency, to an increased risk of hemolytic anaemia and of methemoglobinemia.

In patients with low or intermediate TLS risk, allopurinol can be used as hypouricaemic agent. Allopurinol is a xanthine analogue that will decrease transformation of xanthine into uric acid.<sup>15</sup> However, if it may limit the risk of urate nephropathy in some patients, allopurinol will also induce an increased xanthine and hypoxanthine serum concentrations. The solubility of these compounds is lower than uric acid's one, and xanthine

nephropathy may therefore develop.<sup>43</sup> This complication is however uncommon and allopurinol is still indicated in this population.

### Prevention of nephrocalcinosis

The prevention of nephrocalcinosis relies on the treatment of hyperphosphataemia and the eviction of any calcium therapy. Concerning prevention or treatment of hyperphosphataemia, only few treatments can be proposed in addition to hydration. Oral phosphates binders are not effective. The persistence of a hyperphosphataemia 4 to 6 hours after initiation of saline infusion should lead to renal replacement therapy. Moreover, it is crucial for the physician to keep in mind that the coexistence of a hyperphosphataemia and of a hypocalcaemia is the signature of calcium phosphates crystals deposition.

### Indication and timing of the renal replacement therapies

Although no study has specifically been performed on this field, renal replacement therapy should probably be started on an emergency basis when hydration fails to produce a prompt metabolic improvement or when AKI develops. Indeed, the prognosis impact of development of an acute kidney injury in this setting has been recently demonstrated.<sup>18</sup> Renal replacement therapy allows both metabolic control and renal protection during TLS. Few case reports and series suggests that phosphates clearance might be higher with sequential dialysis than with hemofiltration. In addition it seems that hemodialysis is frequently associated with a rebound effect after dialysis.<sup>8</sup> Moreover, hemofiltration might be unable to produce an efficient metabolic control during the most severe TLS. Therefore, extended daily dialysis or isolated sequential dialysis followed by continuous hemofiltration should be the standard of care for TLS requiring renal replacement therapy. A study is currently ongoing to precise pharmacokinetic of cancer chemotherapies during renal replacement therapy.

### CONCLUSION

TLS is a frequent and a life-threatening complication of the newly diagnosed malignancies. Development of an acute kidney injury or metabolic derangements may lead to ICU admission. However, it is critical for physician to prevent clinical TLS, a condition associated with a poor prognosis. Preventive measures, including prophylactic renal replacement therapy, are required in way to prevent or

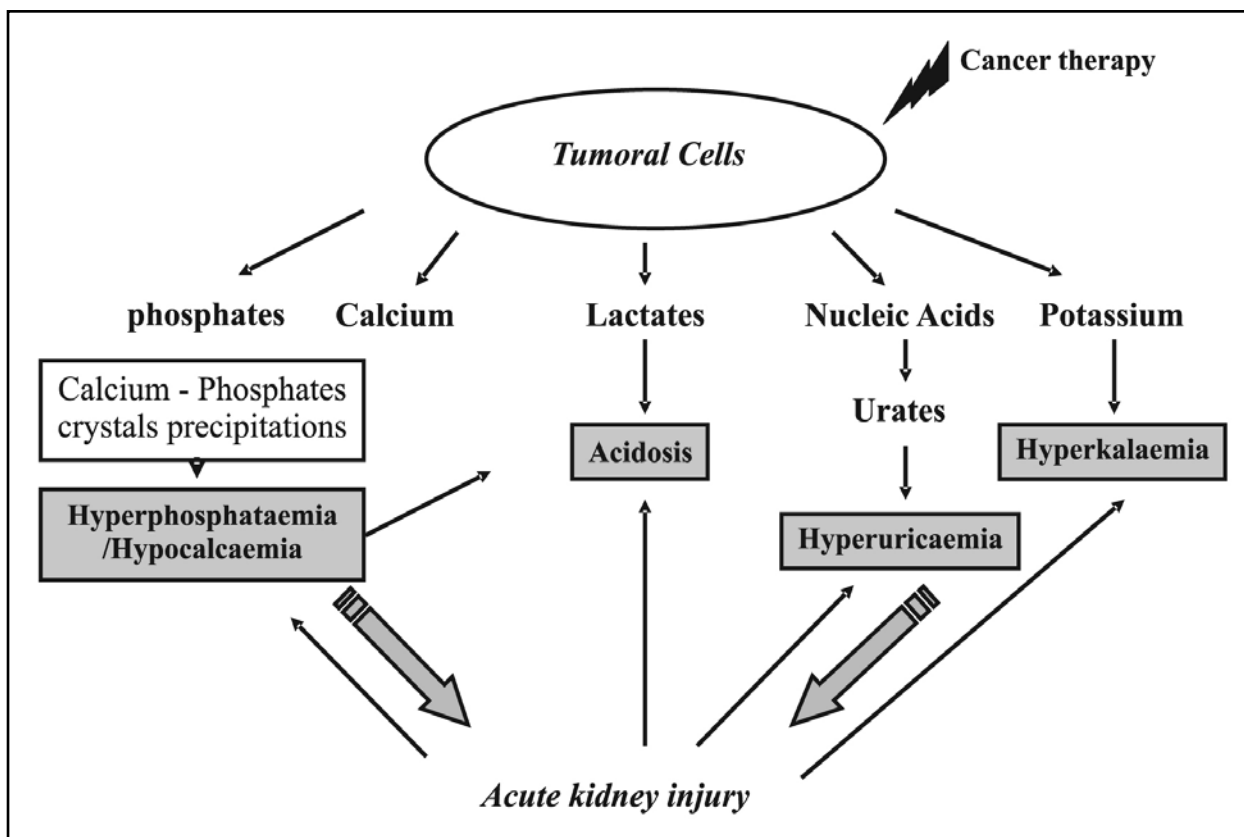


Figure 1 – Pathophysiology of the tumor lysis syndrome.

limit clinical consequences of TLS. However optimal timing and modalities of prevention remains unknown and may be modified by the changing spectrum of patients at risk of TLS. Development and validation of risk based strategies is required in way to limit the high morbidity and mortality of this complication.

## RESUMO

A síndrome de lise tumoral é caracterizada pela destruição maciça de células malignas e a consequente liberação do seu conteúdo no espaço extracelular. Embora possa ocorrer de modo espontâneo, a síndrome de lise tumoral ocorre geralmente logo após o início do tratamento com agentes quimioterápicos citotóxicos. Uma vez liberados, estes metabólitos podem extrapolar os mecanismos homeostáticos resultando em hiperuricemia, hipercalemia, hiperfosfatemia, e hipocalcemia. Estas alterações biológicas podem levar a ocorrência de diversas manifestações clínicas incluindo injúria renal aguda, convulsões e morte súbita que podem exigir cuidados intensivos. Uma vez que a síndrome de lise tumoral está associada a um pior prognóstico, a prevenção de sua ocorrência *per se* e também de suas consequências é mandatória. O objetivo desta revisão foi descrever os mecanismos fisiopatológicos, e as manifestações clínicas e biológicas da

síndrome de lise tumoral aguda, e fornecer recomendações atualizadas para a sua prevenção. Foram selecionados artigos sobre síndrome de lise tumoral publicados nos últimos 20 anos no PubMed ([www.pubmed.gov](http://www.pubmed.gov)). Estudos referenciados nos artigos selecionados na busca também foram utilizados. A síndrome de lise tumoral é uma complicação grave e freqüente em a pacientes com neoplasias de diagnóstico recente. Estratégias de prevenção que incluem hidratação vigorosa, agentes uricolíticos, identificação dos fatores predisponentes a injúria renal aguda e, nos pacientes mais graves, na indicação profilática de métodos de substituição da função renal. São necessárias para prevenir ou limitar as suas consequências. Entretanto, o tempo mais adequado assim as que modalidades de prevenção a serem oferecidas ainda são desconhecidas e podem ser inclusive modificadas por alterações do espectro de pacientes em risco de desenvolvê-la. O desenvolvimento e a validação de estratégias baseadas no risco do pacientes são necessárias para limitar a alta morbidade e mortalidade desta complicação.

**Descritores:** Síndrome de lise tumoral; Antineoplásicos/efeitos adversos; Hiperfosfatemia; Hipercalemia, Hiperuricemia; Insuficiência renal aguda; Leucemia, Linfoma não-Hodgkin; Unidades de terapia intensiva; Nefropatias/etiologia; Acido úrico/efeitos adversos

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