CLINICAL STUDY

# The analysis of the risks for the development of tumour lysis syndrome in children

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**Abstract**

***Background:*** **Acute renal failure (ARF) during the course of cytostatic therapy is a serious complication. ARF can be isolated or became as component of tumour lysis syndrome (TLS). TLS comprises a number of metabolic abnormalities (hyperuricemia, hyperphosphatemia, hyperkalemia, azotemia and hypocalcemia) which are associated with lymphoproliferative malignancies following spontaneous or chemotherapy-induced cytolysis. There exist probably no clear prediction for the development of TLS that could enable early detection of manifestation of this severe condition.**
***Subjective:*** **Conventional management with aggressive hydration, alkalization of the urine, administration of allopurinol, and the slow introduction of chemotherapy is often unable to prevent metabolic instability and ARF. Recent studies define a subgroup of patients at higher risk of renal failure during induction chemotherapy. ARF was encountered during initial therapy of patients with a lactate dehydrogenase (LDH) index greater than 3.3.**
***Methods and material:*** **A retrospective analysis of 10 children (3 girls, 7 boys, average age 9.7 years) with LDH index greater than 3.3 has been done. All children were treated for lymphoproliferative malignancy with conventional preventive measures.**
***Results:*** **Three children needed haemodialysis – 2 boys had fully expressed TLS with ARF shortly after starting chemotherapy, in 1 boy the dialysis was indicated because of extreme hyperuricemia and high creatinine level presented before chemotherapy. We consider that LDH index is not specific criterium for prediction of TLS. In conclusion, our cases demonstrate the pathophysiologic spectrum of ARF in TLS between hyperuricemia and hyperphosphatemia.**
***Conclusion:*** **The LDH index, urine output, and hyperphosphatemia could be used to identify those paediatric patients who would benefit from the prospective use some of extracorporeal elimination methods. Further investigation of this techniques in a larger number of patients is warranted.** ***(Tab. 5, Ref. 12.)***
**Key words: tumour lysis syndrome, therapy, preventive measures, childhood.**

Antitumour chemotherapy has its unique place in the therapy for children's tumour diseases. However, its side-effects represent a certain disadvantage of this treatment. During cytostatic therapy, the kidneys become damaged either directly by the toxicity of the drugs used, or indirectly due to a rapid disintegration of a tumour. Tumour lysis syndrome (TLS) belongs to severe complication of chemotherapy. TLS is characterized (2, 4, 6, 7, 10, 12) by hyperkalemia, hyperphosphatemia, hyperuricemia combined with acute renal failure (ARF). ARF in TLS is usually caused by rapid increase of serum concentration of uric acid (UA) and/or its decreased renal excretion. Consequently, a precipitation of urate crystals that provoke the obstruction of the renal tubules. In some cases, ARF is presented in spite of the fact that the serum concentration of UA in increased only slightly. That occurs particularly when the serum concentration of phosphorus is increased enormously (4, 6). Hyperphosphatemia contributes

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**Tab. 1. Patient clinical and laboratory date at presentation.**

| Pt | Gender | Age (years) | Dg | WBC ($x10^9$/l) | $Cr_S$ (μmol/l) | $UA_S$ (μmol/l) | LDH index | $PO_{4S}$ (mmol/l) | Diuresis (ml/kg/h) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 1.5 | TALL | 393 | 77.5 | 655.8 | 32.2 | 2.05 | 3.8 |
| 2 | F | 11.0 | TALL | 398 | 69.7 | 93.7 | 6.7 | 2.02 | 1.4 |
| 3 | M | 5.0 | TALL | 229 | 53.8 | 354.8 | 5.4 | 1.98 | 2.3 |
| 4 | M | 5.0 | TALL | 132 | 63.6 | 395.2 | 6.0 | 1.82 | 8.5 |
| 5 | F | 11.0 | ALL | 91 | 55.4 | 252.4 | 4.2 | 1.79 | 4.2 |
| 6 | M | 1.5 | ALL | 35 | 96.7 | 518.6 | 5.4 | 1.92 | 2.3 |
| 7 | F | 14.0 | ALL | 69 | 79.4 | 435.4 | 5.5 | 1.57 | 3.2 |
| 8 | M | 10.0 | NHL | 58 | 98.7 | 435.8 | 6.6 | 3.45 | 0.8 |
| 9 | M | 9.0 | NHL | 23 | 121.6 | 524.8 | 6.9 | 3.56 | 0.7 |
| 10 | M | 15.0 | ALL | 14 | 137.4 | 2120.6 | 9.5 | 2.14 | 1.8 |

WBC – white blood cell count, $CR_S$ – serum level of creatinine, $UA_S$ – serum level of uric acid, $PO_{4S}$ – serum level of phosphate, TALL – T-cell acute lymphoblastic leukemia, NHL – non Hodgkin's lymphoma, ALL – acute lymphoblastic leukemia common type, M – male, F – female

to the precipitation of calcium-phosphate complexes in both the interstitium of the kidneys and in the tubules.

TLS is most often seen in patients with lymphoproliferative tumours, marked leukocytosis and/or a large extent of tumour mass. TLS induction occurs at the initiation of the therapy by means of cytostatics/radiotherapy, but also used to prevent the rise of TLS in children (Tab. 5). However, the effective methods of preventing the development of TLS in high risk patients have been still unknown. Published data (6, 11) have indicated the possibility of predicting TLS on the base of calculating the lactate dehydrogenase index (LDH index). The value of LDH index above 3.3 is considered as a risk factor for the TLS rise.

In present study, a set of patients with supposed risk of the TLS development was subjected to a retrospective analysis. Based on our experience, the aim was, with respect to literary data, to consider some parameters that would allow a more precise prediction of the TLS development.

## Material and methods

The set analysed consisted of 10 children (3 girls, 7 boys), aged 1.5–15 years (mean 9.7 years) treated for lymphoproliferative malignity. 8 children (3 girls, 5 boys) were treated for acute lymphoblastic leukemia (ALL), 2 boys for non-Hodgkin's lymphoma (NHL). The criterium for involving the children into the set was the value of LDH index above 3.3. The LDH index is a ratio of the total value of the serum LDH (cLDH) concentration at establishing the diagnosis of the underlying disease to the upper limit of the cLDH norm (LDH index = initial cLDH/upper limit of the cLDH norm). The characteristics of the set of children are given in Table 1. The calculation of creatinine clearance (Ccr) according to Schwartz (CCr/ml/sec = height (cm) x 0.808/serum creatinine (μmol/l) was used for evaluating the functional condition of the kidneys. The CCr value calculated by this way was within the normal limits in all the children. Routine preventive measures against the TLS development were applied in all the patients of our set.

**Tab. 2. Development of TLS and serum concentrations of $PO_4$.**

| Complications | Number of children | $PO_{4S}$ (mmol/l) mean | $PO_{4S}$ (mmol/l) 95 % interval |
|---|---|---|---|
| no | 7 | 1.87 | 1.81–1.93 |
| yes | 3 | 3.05 | 2.85–3.25 |

Legend: complications – necessity of dialysis, 95 % interval – mean±1.96 sigma, $PO_{4S}$ – serum concentration of phosphates

## Results

In the retrospectively evaluated set of children in whom TLS could be expected (the value of LDH index above 3.3), TLS appeared in 3 subjects (patients 8, 9, 10). Here, TLS was manifested in two of these children (patients 8, 9) shortly after starting cytostatic treatment, and oliguria was expressed simultaneously in the two patients. TLS developed spontaneously in one child (patient 10), namely before establishing the diagnosis of ALL.

All the 3 children with TLS required a transitory therapy by haemodialysis (machine Gambro AK 100, double-needle dialysis). This extracorporeal elimination technique was not accompanied by any complications, its mean duration was 14.6 hours, and after its termination, further anti-tumour treatment could continue.

Although the size of our set does not fulfil statistical criteria of representativeness, we do believe that the value of the LDH index represents a little predicting marker for the TLS rise. Statistical methods were used for creating two groups of patients in the set evaluated, according to the factor "necessity of dialysis". The application of extracorporeal elimination technique was considered a manifestation of complicated course of TLS. The hypothesis about conformity of groups formed by that way was rejected on the level of 0.007. The testing of the evaluated laboratory data and the size of diuresis in this set revealed the differences between these two groups of children, both in the levels of the serum concentration of phosphates and the amount of diuresis. Tables 2 and 3 involve a column called 95 % interval which

**Tab. 3. Development of TLS and size of diuresis.**

| Complications | Number of children | mean | Diuresis (ml/kg/h) 95 % interval |
|---|---|---|---|
| no | 7 | 3.67 | 2.39–4.96 |
| yes | 3 | 1.1 | 0.15–2.25 |

Legend: complications – necessity of dialysis, 95 % interval – mean±1.96 sigma

contains 95 % interval of reliability for the estimation of the mean value of the phopsphate serum concentration/lower diuresis at the given factor "necessity of dialysis". Hyperphosphatemia and/ /or amount of diuresis are two other parameters that can be, besides the value of the LDH index, followed up for the early prediction of TLS.

## Discussion

Even Virchow has mentioned the increased serum concentration of UA in diseases accompanied by a great disintegration of cells. However, a case of oligoanuric renal failure at TLS was described as late as 1929 (6). In most cases of ALL within TLS, renal failure is caused by the obstruction of urinary canals with the UA crystals. These crystals are also found in the collecting tubules of the kidney and deep in the cortical and medullary renal vessels. Peritubular granulomatous reaction can be often observed as well. Phagocytosis of the UA crystals by the epithelial cells of urinary canals is proved by the presence of crystals in lysosomes or cytosol. The primary functional abnormity leading to azotemia and oligoanuria at urate nephropathy is intraluminar tubular obstruction, vascular obstruction can also share in the loss of filtration capacity of the kidneys. Large amounts of the purines, metabolites of phosphates and other intracellular substances are not only a harbinger of the TLS rise, but they contribute to the renal function failure by creating crystals and deposits in the urinary canals and capillaries. Urine concentrations of UA are much important than the serum levels because there exists the direct correlation between urine concentration and precipitation of the UA crystals.

Hyperphosphatemia is another metabolic change in TLS which can also contribute to ASL. Hypocalcemia often accompanies hyperphosphatemia and causes of the precipitaion of calcium-phosphate complexes within the kidney. The therapy for hypocalcemia in patients with hyperphosphatemia can provoke metastacic calcification, including intrarenal calcification in the form of nephrocalcinosis or nephrolithiasis. TLS is accompanied with decreased re-absorption of phosphates in the proximal renal tubule, probably due to the higher level of parathormone induced by hypocalcemia. Only these patients show the increased excretion of phosphates which increase the risk of nephrocalcinosis and tubular obstruction by the precipitation of calcium-phosphate crystals. Simultaneous development of metabolic acidosis can induce the shift of phosphates from the intracellular to extracellular spaces. That results in further increase of the plasma concentration of phosphates and their increased supply to the kidneys.

**Tab. 4. Indications for dialysis in TLS.**

| |
|---|
| Hyperkalemia |
| Hyperhydration, volume overload |
| Hypercalcemia |
| Hyperuricemia |
| Control of uremia |

**Tab. 5. Management of TLS.**

| | |
|---|---|
| Hydration | 0.45 NS+5% glucose, 3000–5000 ml/m$^2$/day |
| Alkalization | 100–200 mmol $NaHCO_3$/m$^2$/day, urine pH 6.5–7.0 |
| Diuresis | Furosemide (1–2 mk/kg IV every 6–8 h) |
| Reduce uric acid | Allopurinol (10 mg/kg/per day divided t.i.d., max 800 mg/per day IV or IM)<br>Urate oxidase (100 U/kg per day) |

Legend: NS – normal saline, $NaHCO_3$ – sodium bicarbonate, IV – intravenous, IM – intramuscular, t.i.d. – three times a day

Similarly, the application of $NaHCO_3$ for the urine alkalization is not free of risks, and can lead to the formation of calcium-phosphate complexes which are less soluble in an alkaline medium. Therefore, the therapy for hypocalcemia is only reserved, due to these connections, for symptomatic patients. "Phosphate binders", similarly to insulin and glucose, are media of choice in the treatment of hyperphosphatemia and hypocalcemia.

It is quite explicit that early preventive measures decrease substantially morbidity and mortality caused by TLS. The peroral intake of adequate quantity of fluids, particularly in children, may be found out with difficulties, and, therefore, fluids must be often administered parenterally. Urine alkalization is another preventive procedure: to maintain the urine pH between 6.5 and 7.0 is optimal.

Diuretics are indicated in patients who have, with corresponding hydration, diuresis below 65 % of intake and no extrarenal loss of fluids (vomiting, diarrhoea).

Allopurinol (4-hydroxypurinol) inhibits xantinoxidase. It is an enzyme (1, 10) catalyzing the transformation of hypoxantin to uric acid, and decreasing UA production. Allopurinol is used routinely, its only disadvantage is peroral medicament form and the fact that accumulated xantin and hypoxantin can precipitate in the urinary canals in the same way as UA does. This problem can be solved by the application of urate oxidase (9). This enzyme (arise by the fermentation of Aspergilus flavus mold) converts UA to allantoin which is water-soluble and decreases the serum concentration of UA as well as the excretion in urine. At present, priority is rather given to recombinant urate oxidase (Rasburicase), which is a tetrameric protein prepared by means of recombinant technology (8). However, it has not been registered in the Czech Republic so far.

Developed TLS in an indication for initiating some of the extracorporeal elimination methods (Tab. 4). It must be stressed that the duration of oligo/anuria before starting dialysis corre-

lates partially with the duration of oligo/anuria in the post dialyzing phase. Thus, the necessity of early initiation of dialysis in indicated patients with TLS has been supported (5). Besides classical haemodialysis, any of the filtration techniques (3, 5, 11) can be also used: continuous arterio-venous (CAVH) or continuous veno-venous (CVVH) haemofiltration or combination of haemofiltration with dialysis – haemodiafiltration. The rapid development of technical backrounds of elimination methods has enable to use them irrespective of age or body weight of the children treated. Each of the techniques has both pros and cons. Up to now, literature has not concluded explicitly which of these techniques should be preferred. The disadvantage of haemodialysis may be a great cardiopulmonary instability of patient with the tendency to the decrease of systemic blood pressure, the technique may be less effective for the correction of hyperuricemia. CAVH is complicated from the view of necessary arterial catetrization, but it does not require particular technical backgrounds. CVVH is sufficiently effective and tolerated best by patients. Preventive application of these techniques is possible, although it is reported on sporadically in literature (11). Therefore, the preventive use of CVVH in patients with high degree probability of the TLS manifestation – positivity of the LDH index, hyperphosphatemia, decreased diuresis – should be always suggested.

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Received February 11, 2002.
Accepted April 20, 2002.