Subtitles and transcriptions

Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.

Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

Tumor lysis syndrome

Prof Lazic: Good evening or good Day or even good Morning. It depends where our colleagues are located. I'm really thankful that I have the opportunity to share our experience, Tumor Lysis Syndrome in children. And I'm happy that I have such a good discussant with myself today. So, the first thing that I'll like to state is that, regarding Haemato-Oncology, since the adults have the higher number of patients, and subsequently, the higher number of studies, we usually translate the data from adults to the children, as well as adolescents and young adults. But we need to be aware that the diagnoses are not always the same, the biology of disease is not the same, and consequently, of course, the therapy. Regarding comorbidities, luckily, they are less present in children, and this is why I'm going to focus today only on Tumor Lysis Syndrome in children. So, what is Tumor Lysis Syndrome? It is a rapid destruction of malignant cells, which leads to the release of intracellular content, and that are nucleic acid, electrolytes and cytokines. That leads to metabolic derangements in systemic circulation, such as hyperuricemia, hyperphosphatemia, hyperkalemia, and secondary hypocalcemia and uremia. From clinical point, we can recognize the Tumor Lysis Syndrome when patients develop renal failure, cardiac arrhythmias, seizures, and unfortunately, the TLS can also lead to death. I'm quite sure that we are all very familiar with this theme or the pathological mechanism, but I will just briefly remind you that uric acid has two mechanisms of degradation. One is crystal-dependent, which leads to the uric acid pH, which favors production of poorly soluble uric acid over soluble urate, which leads to the higher precipitation of intratubular crystals. And then, we have the crystal-independent mechanism where three major things are happening. The vascular smooth muscle releases inflammatory cytokines, which leads to the chemotaxis of white blood cells. Also, we can inhibit proximal tubule cells proliferation, which can prolong the acute renal failure duration. And there is a scavenge bioavailable acid monoxide, which leads to the vasoconstriction. In parallel, we have metabolic disturbances, which are leading to the rearranged levels of major ions from the cell, And, of course, the different ranges of osmolality, as well as in blood, as in urine. What about the incidences? It is not still well-defined because we have the historical lack of standardized diagnostic criteria. There is a variability of patient population, as previously said, the data are combined from adults and children. And due to that, we have the three different treatment regimens. So, nowadays in the literature, we can find a huge variety of data. So, the incidence rate from over 4% to over 50%. Majority of patients are diagnosed with laboratory tumor lysis syndrome. And there is a report for low and middle-income countries who states that they diagnose around 16% of children with clinical TLS. Mortality in children is reported to be a little bit over of 20%. And what is interesting that tumor lysis syndrome is uncommon in relapse and chemo-resistant malignancies, but that can be easily explained because they have lower proliferation rate. The criteria was originally established in 1993, by Hande and Garrow, and they classify the basic change in laboratories, 25% from the upper or lower limit of normal, and within four days after the initiation of chemotherapy. There were also the first one to distinguish the laboratory and clinical TLS. The first revision came 10 years afterward, by Cairo and Bishop, and they're the most cited authors who more precisely define the laboratory TLS as at least two isolated metabolic derangements, who can happen three days prior and up to seven days after the chemotherapy initiation. So,

they're actually the first ones who introduced the new terminology, spontaneous, which, of course, is happening prior to the chemotherapy, verses chemotherapy-induced. And they also reported that TLS is mostly seen on the second or third date after chemotherapy initiation. Regarding laboratory TLS, we have four elements. The values are put in different units, and regarding uric acid, potassium and phosphorus, we can see increase above mentioned units, or about 25%, and can see the decrease in calcium levels, or below 25% from the baseline. What about clinical TLS? We grade it from 0 to 5. 0 is absent, 5 is Death, so, we are actually grading from 1 to 4. And the laboratory TLS needs to be present. Then we are looking at Azotemia, if you have the increase in creatinine levels, and regarding the measurement of increasement, then we grade the clinical TLS according to creatinine. There are also two clinical conditions that contribute to it: they're arrhythmia and seizures. So, we have three systems, renal, cardiac, and neurological involved. Regarding cardiac, so we have arrhythmia, which can be ranged from indication not indicated to the non-urgent medical intervention. When we have medical control when we need to control it with device, and when the patient can end up with a heart failure, hypertension, and shock. Regarding neurological deterioration, we can have one brief, generalized seizure or well-controlled repeated seizures. We have the grade-3 when we have altered consciousness, when we cannot medically control the seizures, and when the patients have developed Tetany. The grade-4 is when we have prolonged, repetitive seizures, when, in between, patients are not being conscious. What is happening nowadays? In the literature, we can see the proposal for a second revision, which is still pending. Some authors reported that two or more metabolic abnormalities can be present simultaneously and can be tumor-unrelated; for example, hypoglycemia can be associated with sepsis. Then, the second statement is regarding 25% change from the baseline. Actually, that can not be clinically significant unless the value is already outside the normal and the removal of these criteria is proposed now. There is also the huge debate regarding hypocalcemia, because it can be secondary phenomenon to hyperphosphatemia, as we all know, but also is good indicator of calcium phosphate binding and its precipitation in tissues. Also, there is a proposal to include LDH because this is the best marker for cell necrosis. And it's very important, not only for TLS risk assessment, as we all know, it is one of the criteria for choice of treatment arms, for example, in trial protocols. In the current era, we see targeted therapies evolving every day and they are very highly effective, and majority of clinicians are choosing them for initial therapy as well. So, nowadays, we can see the tumors, who are previously rarely associated with TLS, are increasingly described in the literature, and that raised the question of morbidity and mortality regarding the TLS. It can be higher because we elect to recognize those kinds of tumors, because we don't start with adequate prophylaxis, and consequently, we delay the treatment. I try to extrapolate these new targeted therapies, which are administered in children. So, we can see here the pharmaceutical background, the classes' affect. They're actually targets, in which malignancies they're used, and we can see, at the right side, the incidence of TLS in those agents, either single or combined, with other therapy. And it varies from 1.7 to even more than 40%. And if there are any questions, please, do pose them in a chat or Question and Answer period.

Dr Mahmoud: Good evening, all. Thank you, Dr Lazic, for the interesting slides. So far, there are no questions from the audience, and we are welcoming any question from them. I just have one question for you regarding the classification of Tumor Lysis Syndrome. If we have, this is just a practical point, if we have high uric acid, isolated high uric acid alone, and we don't have any other metabolic derangement, should we consider this as a Tumor Lysis, knowing that we are going to give medication any way or to give a treatment? So, how can we define this? Is it Tumor Lysis or not? Are we going to treat or not?

Prof Lazic: Thank you for this excellent question because trying to systematize many things in medicine is important, but each patient has his story. So, if you are sure that the patient has only isolated hyperuricemia can be contributed to the tumor, not previous, some previous condition, then, I would start for the beginning, maybe allopurinol or even rasburicase to prevent other metabolic disturbances that can occur with hyperuricemia. And of course, the hyperhydration, which is the baseline of prophylaxis and treatment.

Dr Mahmoud: Thank you. Also, I have one more question. Regarding the rising incidence, in the tumors which are not known to have a tumor lysis, is this tumor lysis happening due to pathology of the tumor itself or due to the target therapy?

Prof Lazic: I think it is happening because these drugs are very efficient, highly efficient and they lead to the rapid destruction of tumor cells. And because they're targeted, we don't see such a quick, for example, myelosuppression as with conventional chemotherapy, but we do see the tumor lysis in it.

Dr Mahmoud: Okay. And we have one question from the audience. I think we can answer this later on. I will tell you. Do we use corrected calcium value to check for hypocalcemia and are there any role for phosphate binders in tumor lysis at all?

Prof Lazic: Yeah, but we can answer it now or we can continue to electrolyte management and... yeah.

Dr Mahmoud: Maybe after treatment, yeah. Dr Laic: Okay. Thank you. So, what about tumor lysis and risk factors? We have characteristics that come from malignancy and we know that lymphoproliferative malignancies with high proliferation are the ones for mostly associated with tumor lysis syndrome. But as well as some solid tumors who have rapid response to the therapy. Also, regarding the disease itself, the bulky disease, which is like tumors who have a bigger diameter of 10-centimeter so widely metastatic disease, the tumors who produce the LDH, which is moderately increasing and the white blood cells above 25,000. But we should never forget the host. So, what are the things without which are patient-related? So, there are preexisting renal disease such as nephropathy, urinary tract obstruction, uremia. The patients who already have oliguria, hypovolemia or hypotension, but when we have the pre-treatment hyperuricemia or hyperphosphatemia. Then we have the concurrent use of some nephrotoxic drugs and baseline uric acid below mentioned level. Above, sorry, not below. And also, we need, as previously said, to look at what kind of drugs we are implementing in the patients. So, there is high-sensitivity either to these new drugs or some conventional drugs as steroids or etoposide, but we should not forget that anesthesia and surgery by themselves can also cause the tumor lysis syndrome. And I will show that later on in some patients of ours. So, what about TLS and Leukemias? Burkitt-Leukemia is always high-risk. ALL has no low-risk. It has intermediate-risk when we have white blood cells below 100 and moderately increased LDH and is high-risk when we have white blood cells below 100, but severely increased LDH or hyperleukocytosis when we have white blood cells above 100. Regarding AML, they can be divided into low and intermediate-risk. Low-risk is when we have white blood cells below 25 and LDH below two times upper limit of normal and intermediate when we have white blood cells below 25 but severe increase in LDH or severe increase in white blood cell count. Chronic Myeloid Leukemia is by definition low-risk for TLS development. What about lymphomas? We have Burkitt type lymphomas, being...do not have also the low-risk for TLS. We have intermediate that is early stage of disease plus LDH who is mildly or moderately elevated. And high risk when we have early stages, severely elevated LDH and advanced stage of the disease. When it comes to the non-Burkitt type of Lymphomas, we have anaplastic large cell lymphoma; low-risk for TLS development is early stage, intermediate, advanced stage. Lymphoblastic lymphoma. Intermediate-risk for TLS is early stage of the disease plus LDH moderately increased. And the high-risk is early stage with severe increase in LDH and advanced stage of the disease. Lymphomas such as Hodgkin, marginal zone, MALT and Cutaneous T-cell are in low-risk of TLS development. Diffuse Large B-cell lymphoma and Primary Testicular Lymphoma are in low-risk for TLS in early stage, intermediate in advanced stage, but moderate increase in LDH and high-risk for TLS when they are advanced stage and with markedly increased LDH. Solid tumors in children are by definition low-risk for TLS development in exception of advanced stage of Germ cell tumors and neuroblastomas. What about renal function? If we have the patient with the good renal function and low-risk disease, we did not upgrade them; when we have a patient with good renal function and intermediate-risk disease, if the uric acid, potassium and calcium are within the normal range, there is change. And if they are increased, then, we upstage those patients to the higher-risk of TLS development. When we have the patients with renal dysfunction and they have a low-risk disease, we upstage them to intermediate. And

when they have intermediate-risk disease, we upstage them to the high-risk of TLS development. Why do we insist that much on renal failure? Because it is a poor prognostic factor, which leads to the preclusion of initial chemotherapy and can have the long-term complication. And here, we can see how the crystals are located in tubules of kidney, enabling them to have a normal function. So, altogether, when we summarize previously said we choose the prophylaxis according to the tumor lysis syndrome risks. So, if there is a minimal, for example, the localized Ewing sarcoma, we do nothing. If there is a low-risk, we administer hydration, allopurinol, and close laboratory clinical monitoring. If there is intermediate-risk, we administer hyperhydration, allopurinol or rasburicase and perform laboratory tests on 8 to 12 hours. If there is a high-risk of TLS development, again, a continuous hyperhydration, rasburicase, cardiac monitoring, including, of course, ACG and laboratory tests on 6 to 8 hours. And if you already have clinical TLS developed, we, of course, give the hydration, rasburicase, cardiac monitoring. If needed, transfer the patient to ICU and have very close laboratory tests monitoring on eventually four hours. What about fluid management in tumor lysis syndrome? We prefer isotonic solutions in pediatric in general. So, it is two to three liters per square meter per day. Intravenously, of course. And this is something like when calculate two times maintenance. In exception of children below 10 kilograms when we give 200 milliliters per kilogram per day. What about urine output? We try to maintain that your raise is between 80 and 100 milliliters per square meter per hour, which is calculated as two to four milliliters per kilogram, per hour. And in smaller children below 10 kilograms, this should be higher, four to six milliliters per kilogram, per hour. Regarding directed therapy, we give it only if necessary to maintain diuresis. Usually, it's not needed in patients who have normal cardiac and renal function. And it's definitely contraindicated with patients with hypovolemia or some urinary tract obstruction. The drug of choice are loop diuretics like Furosemide not only because they induce diuresis but they also contribute to increase potassium secretion. The dose ranges between 0.5 and 2 milligrams per kilogram IV. And I would say I would prefer the lower dose because we should not forget that diuretics are nephrotoxic as well. And there is one Hamlet's dilemma from the past about urine alkalization. So, to alkalinize or not? in the past the Acetazolamide or sodium bicarbonate were given to maintain the urine pH of 6.5 to 7 or even higher. And it was recommended to alkalinize to increase uric acid solubility. Novel findings are showing that these measures did not demonstrate enough efficacy. In contrast, there is a likelihood for uric acid precipitation in the tubules for the promotion of calcium phosphate deposition in kidneys, in patients with marked hyperphosphatemia. And also, these measures can favor calcium binding to albumin, which is decreasing ionized calcium concentration. What do we do with electrolyte management? If we have hyperphosphatemia, we should, if it is moderate, we should avoid IV or PO phosphate administration. We can administer Aluminum Hydroxide, I must say that we usually do not give it, and if you cannot control it by these measures, we can start the dialysis. Regarding hypocalcemia, if it's asymptomatic, then, we do nothing, so no therapy; if it is symptomatic, we start the cardiac monitoring, do the ECG. And we can administer calcium gluconate or calcium chloride. When we have hyperkalemia, if it's moderate, we should, of course, avoid the intake of potassium either intravenously or per oral. We put the patient on cardiac monitoring and we can administer sodium polystyrene sulfonate. We can, in case of severe hyperkalemia, we can administer calcium gluconate in much higher doses than for hypocalcemia, we can give insulin and 25% solution of dextrose. We can give inhalation of salbutamol. We can administer Bicarbonates. And if these measures do not work, we can start the dialysis. What are the drugs indicated? The first and the older one is allopurinol, who can be given per orally or intravenously. If we give per orally, it's divided in three daily doses on each 8-hours, week duration is usually between 3 and 8 days. And the maximum daily dosage is 800 milligrams per day. If you give it intravenously, it is the same dose and regime and duration. It can be reconstituted with isotonic glucose or sodium chlorate. It is incompatible with bicarbonates, and the maximum daily dosage is 600 milligrams. Allopurinol should be reduced when we have the renal failure. And there is a table how we should decrease the dosage of allopurinol by glomerular filtration rate of...or clearance, creatinine clearance. If we are giving concomitantly the purine allopurinol or azathioprine, they need to be reduced up to three quarters of dosage, we also need to adjust if concomitant therapy with thiazide or loop diuretics, cyclophosphamide, high-dose methotrexate, Cyclosporin, some antibiotics or anti-epileptic drugs.

Allopurinol can cause hypersensitive reactions such as like vasculitis or Steven Johnson syndrome. And especially, in certain Asian population who are carriers of this allele. Rasburicase is more novel, but not really the new drug. And its dosage is 0.1 in low-risk of TLS. And there is our clinical judgment, how long we will give it, or should we repeat it? In intermediate-risk patient the dosage is 0.15 and the continuation of rasburicase is based on uric acid level. And in high-risk patient the dosage is 0.2. And it's also the duration of therapy-based of uric acid levels. It is administered intravenously over 30 minutes. The average is from 1 dose up to 7 days, and it's contraindicated in GCPD deficiency due to hydrogen peroxide, which is the by-product of uric acid breakdown. And it could cause anaphylaxis and also hypersensitive and hemolytic reaction. The special caution about rasburicase therapy is antibody formation. In about 10% of patients also methemoglobinemia was reported, and there is not enough data on teratogenicity of rasburicase. So, what happens when nucleic acid breakdown? It starts the purine catabolism leading to development of hypoxanthine and xanthine leading to production of uric acid. These two points are the moments when allopurinol, which is considered xanthine oxidase inhibitor reacts and reacts via its active metabolite, which is oxypurinol. But we need to be cautious because allopurinol has no effect on pre-existing elevated uric acid. And usually, when we start the therapy, we need three to four days to normalize the level of uric acid. Uric acid is the endpoint in humans and it's created in urine and has very low solubility. Here comes the rasburicase. This is urate uricase oxidase, which converts the uric acid to water soluble Allantoin which is not constitutively, as I said, present in humans is high-soluble and can be excreted in urine. So, there is a new kid on the block, as the song said and there is a new drug in the market that is also a Xanthine oxidase inhibitor as allopurinol, but it's not purine base analog as allopurinol is. It has minimal effects on other enzymes involved in purine and pyrimidine metabolism. It's relatively new, a little bit more expensive, probably due to the fact that there is no generic preparation, and it showed that is not causing hypersensitivity reactions like allopurinol. The major study was done in adults, were randomized, it's called FLORENCE. And where the patients were randomized to receive febuxostat versus allopurinol, and they showed the better control of hyperuricemia, good safety profile and preservation of renal function, but they didn't show that the febuxostat lowers the creatinine level and the side effect of this therapy had the greater incidence of liver dysfunction, nausea and joint pain. The pediatric reports' cards, I think only two or three studies. And they reported that they gave the much lesser dosage than in adults. So, 10 milligrams versus 120 and the results are quite similar like in adults. What are the guidelines for dialysis use? The severe oliguria or anuria or intractable fluid overload persistent hyperphosphatemia or hyperkalemia, symptomatic hypocalcemia and calcium-phosphate product over 70. With the introduction of rasburicase the need for dialysis really reduced greatly. And around 3% of patients, 1.5% of small treatments, and 5% of adolescent and young adults are in need for dialysis. I need to underline that the methods of choice, there are several methods for renal replacement therapy, of course, and the method of choice can be hemodialysis, peritoneal dialysis is almost never used, and it's very efficient in removing uric acid, ensure the clearance of 70 to 100 milliliters per milliliter and the decreases the level of uric acid by 50% with each course. Some dialysis can last two, four or even six hours. And I really encourage you to ask questions. Dr Mahmoud?

Dr Mahmoud: Yeah, we can go back to the last question. Should we use the corrected calcium value to check for hypocalcemia? And also, are there any role of phosphate binder in TLS syndrome? Now, just add one more question about your experience in using polymeric phosphate binder in your practice.

Prof Lazic: Yes. Okay. Yes. If you are not, how to say, if you choose one method to track the results, then this method should be, with this method you should continue, if you use just level of calcium in the blood, that is something that you track further on. And if you choose to calculate or choose to track the ionized calcium in, for example, gas blood analyzers, that is the way to go. So not, I saw that people try to be sure of the result and the measures that already introduced to the patients and they mix the methods for tracking and monitoring the levels of metabolites and this is something that should not be recommended. So, if you choose just the regular level of calcium, this is also okay. You don't need to calculate, if you choose to

calculate, just continue with that. Yeah. Sorry, the second question was? Dr. Mahmoud: Phosphate binder and sevelamer, your experience.

Prof Lazic: Yeah, the sevelamer. Yes. The sevelamer is unfortunately not registered in Serbia. We give it off-label, and our nephrologists are very happy with the results with it. But what is about, what about sevelamer in our patients? It takes time. It is good for patients who have the underline and nephrological disease and renal problems because they had time. But usually, in patients with tumor lysis syndrome, you need to decrease the hypophosphatemia quickly. So, you need time for sevelamer to act. So, what we do, we can give super-maximal dosage, but there is, of course, a danger of severe diarrhea, which sevelamer can cause. But my experience is that the patients who needed sevelamer had also other metabolic disturbances and eventually ended up in the dialysis.

Dr Mahmoud: Okay, this is great. This is actually the same experience. It takes time to lower down phosphate level. Maybe, it is more useful in patients with renal impairment but in patients with tumor lysis it takes some time, and this is exactly what we experienced with it.

Prof Lazic: It is very safe drug. And it also helps to increase the calcium level. And, but we can also give the calcium carbonate instead, and it also binds the phosphorus and help the increase of calcium as well.

Dr Mahmoud: Yeah, there is another question from the audience, what about intravenous fluid reduction in oliguric or anuric patients for a fear of multi-overloads?

Prof Lazic: I would not do that because if you have oliguric patient, the first thing that I will do in almost anybody, in exception of patients who cannot be overload with fluid due to cardiac problems. And usually, they're not the children. I will force the hydration because one of the first methods to maintain the good diereses is fluid, not diuretics. Diuretics are second or even the third step that we take. So, if I judge, if the patient is like developing pulmonary edema or his heart cannot, how to say, the heart condition cannot be saved in hyperhydration, that is the moment when I will reduce the hyperhydration. But in all other cases, no.

Dr Mahmoud: Yeah, we have to, we have to be very strict with fluid balance. In this case, I would encourage, like you said, dialysis, I'd give some diuretics, but I will never reduce fluids unless we have a severe overload, like Berlin edema also. We have to be cautious with antibiotics, which is given in other [Audio Not Clear] to be inclusive in the flow chart. And it's the most important thing, is to have a stick fluid balance, maybe every 6 or every 8 hours to check the negative apport fluid balance and act accordingly.

Prof Lazic: And also, we need dialysis. And you, you raise a very good point because people usually when they calculate, they just calculate the intravenous re-imputation not calculate the other drugs who are reconstituted in some liquid. And also, we need to be aware that the patients could develop tumor lysis syndrome. There is, just imagine the tumor who is floating. So, this is like tumor in their circulation. And if you reduce the hydration, then it's not good for the blood vessels. And it's not definitely something that I will do as the first measure in exception of this conditions that we already mentioned like pulmonary edema or some heart condition.

Dr Mahmoud: Yeah, of course it is theoretically easy. It was easy. But during the practice, it's very hard, especially when you are giving this patient a blood transfusion and a lot of medications. So, it is yeah, it is hard to manage this, but we can act according to the fluid balance and in and out.

Prof Lazic: Sure. And in high-risk patients, you monitor diuresis hourly. I mean, you should not...

Dr Mahmoud: Yeah, exactly. Okay. We can go on with the presentation.

Prof Lazic: Thank you. So, I would like to share with you our experience. So, this is a single center experience from University Children's Hospital, my hospital, and we have collected in the last five years from 2015 to

2020, 167 patients with lymphoproliferative malignancies, the majority of them, like two thirds, were diagnosed with acute lymphoblastic leukemia. One quarter renal Hodgkin's lymphoma and 16% with acute myeloid leukemia. There were slight predominance of male gender. And the average age was 8 and the median 6.6 years. The striking point for me is that we diagnose the patients in advanced disease. So, regarding ALL, majority of patients were stratified to intermediate and high-risk groups. Regarding AML, it's the same story. And especially, in non-Hodgkin lymphoma patients the majority were diagnosed in advanced stage of their disease. So, 20 patients out of 167 developed tumor lysis syndrome, which is around 12%. So, Serbia is upper middle-income country. And we tried to see and compare our results with the published studies and what I've found, two different studies from Pakistan, which is also the middle income-country where they reported much higher incidence of TLS in their patients. And maybe, Ehab can comment later on, on that. I also found the data from Ethiopia who is also middle-income country with a three times higher TLS incidents and Saudi Arabia. The country that they have is working and which has the most similar incidence of TLS in their patients. To come back to our patients. The induced TLS was seeing in the majority of patients, 80% and on day one, around little less than a third of patients developed TLS on day two, a little bit more than a third of the patients. And on days between 3 and 6, also, a little bit more than 30% developed the tumor lysis syndrome. The average from chemotherapy initiation was 2.5 days, which is really very similar to the literature report, half of our patients, so 10 patients, develop laboratory and 10 patients developed clinical TLS. What was the course of clinical TLS? All patients who develop clinical TLS developed also acute renal failure. And we apply the renal replacement therapy in 4 out of 10 patients and they're all alive. Our choice for renal replacement therapy is mostly chemodialysis for stable patients. And for patients who are unstable and especially the ones who require mechanical ventilation, we chose, I mean, in agreements with our nephrologist, of course, the hemodiafiltration. I need to underline that unfortunately, we cannot apply rasburicase. We don't have it in Serbia. And I believe that this number will be lower if we had the rasburicase to give regularly. And I forgot to say, I am sorry, that two patients develop seizures and five patients develop arrhythmia. How was the disease look like in our patients? So, we had a boy with bulky mass, diagnosed with Burkitt lymphoma. We also had a boy with a huge T-cell lymphoblastic lymphoma. And we have the patient with Burkitt who developed TLS prior to the treatment because in regional hospital, he was admitted on a suspicion with some intestinal obstruction. He underwent the surgery. And that was the moment when he developed TLS and was immediately transferred to our center in very bad clinical condition. He also developed, in the local center, the compartment syndrome, and we needed to perform the surgery to save his arm. He also developed DQ, that was the child in whom I saw the highest calcium level in my life. It was 11.5 and he survived. And I would like to conclude with the three-key points. First one is prevention. We need to be aware of tumor lysis syndrome and to recognize it quite early; we need to have precise TLS risk-stratification because due to it, we apply the adequate prophylaxis. Regarding the intervention. We need to have vigilant laboratory and clinical monitoring We need to have vigilant laboratory and clinical monitoring in order to minimize the complications from tumor lysis syndrome and disease itself. And also, we need to be honest to ourselves as our center provides multi-disciplinary team members, like we cannot do that by ourselves. We need intensive care specialists. We need nephrologists. We need facilities like laboratory and dialysis. And also, for the future, we need to enhance the collaboration between clinic and laboratory to develop even more predictive algorithms in our patients. And with this point, I will complete my talk.

Dr Mahmoud: Again, thank you for an informative talk and as mentioned tumor lysis is always a top pediatric oncology emergency, and it's also a condition that requires a multidisciplinary team approach with both, of course, general pediatrics, and intensivists, nephrologists. The good thing about tumor lysis syndrome, it's a highly predictable condition and easily preventable provided that all supportive care settings are present. Regarding treatment I can confidently say that rasburicase is a breakthrough medication the setting of tumor lysis syndrome, and fortunately from those who developed tumor lysis syndrome we have no single case by out of it, not require more invasive interventions like dialysis or so in our center over the last 15 years. I can see no questions. We can encourage the audience to post the questions at the Question-and-Answer icon.

Meanwhile, I have some questions for you. First thing, what do you think about hypokalemia during the induction phase or even pre -treatment in leukemia or lymphoma patients? We usually see patients who are coming with tumor lysis. Yes. And also, maybe more than 50% of these patients have a potassium level less than 3 or even less than 2.5. So, how can we treat these patients? Are we going to treat or not?

Prof Lazic: Well, we usually thank you for this question because it is very frequent, metabolic disturbance that we also see, we usually call it washed hypokalemia because it is mostly often caused by hyperhydration. So, we wash the calcium from the patient. And I would say the level of calcium is below 2.5. Then, I would revise the previous restriction or food enrich with calcium. Because when we start, when we recognize the tumor lysis syndrome, we had the good nutrition support from our nutritionist so that each child receives the food who are not enriched in phosphate, in calcium, et cetera. And if the calcium is below 2.5, I will then try to revise this for the intake. So, I will give the food who is rich with the calcium, and if it stays low, I will choose to give bowls. Is that, or put the calcium in continuous intravenous re-hydration. I would rather choose the bowls, but if I need to frequently repeat the bowls, of course, then we need to include calcium. There is, of course, no need to underline that we need close clinical and laboratory monitoring. And especially, the hypokalemia is, how to say, the patients could develop bowel problems like hyperperistalsis, are in danger of hyperkalemia. So, this is the moment when I will include the calcium in continuous, for example, in continuous intravenous re-hydration. But I will always rather choose bowls or first drive with oral intake.

Dr Mahmoud: Yeah, exactly. Almost the same experience here. From 2.5 to 3 we are not usually correcting potassium and less than 2.5, we are usually giving rapid correction over 4 hours or so with frequent monitoring of potassium level, and also, revise things, with oral intake. Okay. What about, as you said, alkalization, is not any more used now in prophylaxis or even treatment of tumor lysis, but what about if we have a patient with persistent acidic urine? Can we still consider alkalinization of urine? Giving bowls or something like that.

Prof Lazic: Well, we can give, but not concomitantly with calcium. We need to be, of course, careful with that. And of course, the bicarbonates are also not very friendly with other solutions. So when we give them, we need to be, you know, to monitor and balance the other employed management. But I cannot really remember. I'm not that old, but sorry I cannot remember, but I think we stopped alkalinization for sure more than five years or even more ago. And we did not to experience any, how to say, prolongation of this, what you just mentioned. We, we didn't see it.

Dr Mahmoud: Okay. I have a couple of questions regarding the rasburicase, about the first one, usually we're giving, usually you're not using a second dose in most cases, the first dose is enough to do the job but what if the uric acid level is reduced? Are we going to a continuous allopurinol or we are just going to stop and monitor?

Prof Lazic: Well, regarding rasburicase, unfortunately, since it is not available in Serbia, my personal experience is limited to the insights which I had during my education abroad. And, but what I understood from the literature is that resistance to rasburicase really appears to be acquired rather than the patients have preexisting antibodies and these anti-rasburicase antibodies induce in vitro clinical refractoriness by inhibiting the enzyme catalytic activity. And it can be shown, in laboratory animals, mostly in mice, that rasburicase can cause transient reduction in B and T-cells, but very robust depletion of rasburicase specific B cells. There is also the range in the literature about reporting the antibodies, the level of antibodies under the level. The occurrence of antibodies in rasburicase, and it ranges from 0 to even 15%. And the presence were mostly monitored on day 7 and day 14 after the treatment, after the first exposure. And what is interestingly that the anaphylaxis occurs most frequently after the second dose. So, that is very complementary about something that you already said is that usually in children one dose is enough and reduces the chance for anaphylaxis as well. But interestingly, there were adult patients, but they try to

investigate, and they saw that hypersensitive reactions and antibody... the patients who develop antibodies did not decrease the enzyme functional activity, which is very, very interesting. And these studies showed that we need to investigate more. So, we need probably to join the experience on rasburicase in children. I don't know, can we draw the parallel, for example, with asparaginase and formation of antibodies and activity, or even with patients with hemophilia who can also develop the antibodies N-factor is practically not comparable, but I think as a model for something that is more familiar to us, that we can use and investigate more about rasburicase antibodies and hypersensitivity reactions.

Dr Mahmoud: Fair enough. And what about Allopurinol? Are we going to resume with allopurinol after reduction of uric acid by the first use of [Audio Not Clear]?

Prof Lazic: Personally, I would not. If you have a good decrease of uric acid, I would just force the hydration and diuresis. Of course, monitor the level of other metabolites. And I don't think that we need to switch. Of course, it depends, we tailor, despite all the criteria and everything else, we tailor the therapy to the patients. So, if the patient maintained the uric acid already decreased from rasburicase, and doesn't decrease it further, then perhaps I will introduce the allopurinol. But if it goes, it needs time again, if it goes down, then I will not rash with allopurinol.

Dr Mahmoud: Yeah. There is one also point regarding the use rasburicase if we are going to collect uric acid after giving rasburicase, we will have to collect it in ice packs because of the degradation of uric acid, maybe, it will give us low results, but it's still high. So, we have to collect it in ice packs and drove it to the laboratory. Okay, you mentioned that there is no need for prophylaxis in minimal tumor lysis syndrome. Okay I know the low, intermediate and high. But what is the definition of minimal? Can we consider leukemia and lymphoma within that particularly?

Prof Lazic: No, no. They, by definition, leukemia, lymphoproliferation malignancies like leukemia and lymphoma cannot be minimal or even low. For example, chronic myeloid leukemia is low, but the other ones are not really. In exception of some types of acute myeloid leukemias. For example, minimal is solid tumor who is localized. For example, if you have rhabdomyosarcoma, Ewing sarcoma in extremity, this is something that, yeah this is something that you would not expect for tumor lysis to develop. But of course, in those patients you also perform the biochemistry and ... yeah.

Dr Mahmoud: So, leukemia and lymphoma, we will never consider as minimal. And we have to give prophylaxis hydration at least with allopurinol even if there is a high-risk, there is no high incidence, there is no tumor burden, we have to consider for prophylaxis.

Prof Lazic: At least for if you have the patients who have really completely normal CBC and biochemistry, and they are, how to say, the suspicion of leukemia came from clinical science. And one of my students really made an excellent work on how many children have normal CBC on diagnosis of acute lymphoblastic leukemia. And that's 2.5%. And of course, but they had something, they have either hepatomegaly, splenomegaly, lymphadenopathy, operative fever, malaise, something. So, some clinical signs. And those patients are really at lower risk for tumor lysis syndrome because don't have high white blood cell count. They do not have elevated uric acid levels, et cetera, but at least hydration per one day. And you can discharge them to the day hospital. Just monitor. If you start with steroids, if the cytotherapy just do not induce the tumor lysis syndrome. Of course, we do not expect that when there is a low burden of disease.

Dr Mahmoud: Okay. One more question regarding the dialysis. Can we consider dialysis with only assistant high creatinine level without presence of oliguria?

Prof Lazic: Not really, the dialysis should be introduced if you cannot medically decrease the phosphate level, for example, or calcium levels. So, it's not only about azotemia. And it's also about the clinical aspect of the patient. If you have severe oliguria, which is below the 0.5 milliliters per kilogram per hour, then, if you force

the diuresis by hydration, by diuretics and you don't accomplish the higher urine output, then, you should consider dialysis. And sometimes, even one course can be enough. Sometimes that helps that you make the clearance of toxic metabolites and just how to say, switch the clinical state in the patient. And then he starts to maintain the good diuresis. And you don't need to continue. I'm sorry. I also wanted to say that our nephrologists actually have, when we discuss what the best approach is in our patient could be, and they even suggested to have in such a patient, dialysis which lasts two hours, but you repeat it in, for example, two, three days, and they think this is better than to have a long-course and then, wait for like outcome of this course you'll have.

Dr Mahmoud: Regarding the incidence, which I've mentioned, in my opinion, I think in Pakistan, and in even low-income countries, I think the incidence is high because the patients are presenting in advanced stages. That's why the diagnosis of tumor lysis syndrome has high incidence. But in some countries, like in Saudi Arabia, the incidence is low because the patients are protected in here, and given prophylaxis and hydration so, maybe the incidence is less because of this. I don't know any other reason.

Prof Lazic: Yeah. I think also the key of success should lie in that that children should be, I mean, throughout their childhood, be monitored by pediatricians. If you have GPs who can be excellent, but cannot really... Yeah. So, I think the countries who have this opportunity to be monitored by pediatricians are in better state. Yeah.

Dr Mahmoud: Okay. I think time is so close, and I would like to thank you again and I would like to thank ESO for this presentation, and wish everybody a good evening. And if you have any other comment?

Prof Lazic: I would like also to thank you because you raised such an interesting question for discussion and was leading this discussion in very good manner. And I would also like to thank ESO for raising this topic as one of the most important in pediatric haemato-oncology.

Dr Mahmoud: Thank you very much.

Prof Lazic: Thank you. Good night.