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Fungal infections during the treatment of childhood cancer

Prof Lehrnbecher: So, good evening, everybody. I will talk as you know about fungal infections during treatment of childhood. These are my conflicts of interest, I think it's important because we will talk also about antimycotics so, therefore, I wanted to bring this up. And the learning objectives are first, we'd like to talk a little bit about the clinical significance of invasive fungal disease, about risk groups and special risk factors. Then, we move on to antifungal compounds, to diagnostics, and last, to different anti-fungal strategies. We'll be talking about prophylaxis, then about empirical and pre-emptive antifungal therapy, as well as about therapy of established infections. When we think about the clinical significance of invasive fungal disease, I will show you some data from Zaoutis which were published in 2006 on invasive aspergillosis. This was a retrospective cohort study, which identified more than 600 pediatric cases of invasive aspergillosis among more than 150,000 immuno-compromised children. And as you can see here, the medium length of hospital stay was significantly longer in those children with invasive aspergillosis compared to those without invasive aspergillosis. I think was the case for the median per-patient hospital charges, 50,000 in those with invasive aspergillosis compared to those 19,000 without invasive aspergillosis. But more importantly, when we look at the mortality here, we see that invasive aspergillosis, significantly increases in-hospital mortality in immunocompromised children, and this is true for different malignancies, especially here, if you can see here, leukemia, ALL, AML, lymphoma, but also here, when you look to the stem cell transplantation. And when we talk later on the antifungal strategies, prophylaxis and pre-emptive therapy specific therapy, we have always have to have in mind, for example, the population at risk, nobody would prophylax somebody who is not at an increased risk for invasive aspergillosis, for example, we have to talk about or to think about local epidemiology, the availability and the value of the diagnostic tests, as well as on the availability of antifungal compounds. And first, I will talk a little bit about the populations at risk. If you, I'm looking here when we look at the pediatric AML patients, and this was a study by Lillian Sung in 2007, you can see here that in all of the different treatment courses, like induction, consolidation, intensification, we have a risk for invasive fungal disease here of more than 10%, here, 18%, even 21% and 14%. And we see here candida infections, aspergillus and less often, that's what then the clinical experience is fusarium and mucor. And we have to say in this patient population here, they could not administer antifungal prophylaxis. Similar data we have in pediatric allo stem cell transplantation. This was a retrospective single-center study in more than 200 children and incidence of invasive fungal disease was 12%. And supporting the data I showed you before, the patients who develop IFD had a significantly increased risk of treatment related to mortality. So, the more complicated it's in pediatric ALL, and this is important because this is the biggest patient population you see and these are confidential data which are unpublished to date. This is an analysis of the AIEOP-BFM ALL 2009 study. We had analyzed more than 6,000 patients, little bit more boys than girls. Then here, there's stratification in the different risk group, SR, the standard risk, one third, MR, a little bit more than 40%, a little

bit more than 20% in the high-risk group. And as you can see here, 93.8% did not have any signs of invasive fungal disease, 2.4%, possible invasive fungal disease and proven or probable. So, we, where we have the, either the different biomarkers and/ or could isolate a specific pathogen so, in 3.8% of the children. So, at the end, we think it's pretty low, but when we look to the incidents rates in different subgroups of patients, and this is an univariate analysis, so, we are just analyzing and try to do a multivariate analysis. We see that if you look only in the high-risk patients, high-risk for leukemia, the percent is 6.8% of the children develop invasive fungal disease. When we look like poor responders, 8.1%. And we look to older patients, like 15 years and older, we are almost 10% of those developing an invasive fungal disease. So, we have really to try to characterize those patients were an increased risk for invasive fungal disease. And this table is basically based on the meta-analysis Brian Fisher did it in 2018. I have here the high-risk patients, and these are defined by at least 10% risk for invasive fungal disease. And, as you remember now, the slides before these are the patients with acute myeloblastic leukemia. Those I didn't show you the data with recurrent acute leukemia's, Allo stem cell transplantation, and some of those patients with high-risk acute lymphoblastic leukemia. In contrast, low-risk, less than 5%, sporadic occurrence in acute lymphoblastic leukemia. And at least, or I would say in most of these patients, but this depends on the protocol and additional risks factors, for example, steroids, also, which kind of steroids with prednisone or it's dexamethasone prolonged granulocytopenia risk of IFD may increase and even exceed more than 10%. And the low-risk and sporadic occurrence you have here in the non-Hodgkin lymphoma, autologous stem cell transplantation, pediatric, solid tumors, brain tumors, and Hodgkin's lymphoma. However, consider that low and sporadic risk is not equal to no-risk. Here, I would like to, just to interrupt and really to remind you that you can ask questions and then comments at any time. So, click on the Q&A button and send your questions and comments. I will be happy to answer those. Moving-on to the antifungal compounds. And I show you here, I mean, these polyenes with the different formulations of amphotericin B, well-known it's the conventional amphotericin B, and the amphotericin B deoxycholate, the Liposomal amphotericin B, AmBisome, in the different formulations or the lipid formulation of amphotericin B. And the Triazoles, fluconazole which is not active against the most, I won't talk a lot about fluconazole and in both, you can see here, those are approved for the pediatric population. And we have itraconazole and voriconazole, posa and isavuconazole which is new, and there are pediatric studies running right now. And we have since like 2004, the echinocandins with caspofungin, micafungin and anidulafungin. And I won't talk about it. The nuclein acid synthesis inhibitors like flucytosine. And this liposomal amphotericin B, you have to say the activity, which I show you here is similar as the conventional amphotericin B and also, the lipid formulation, but this has liposomal has the better tolerability. And compared to this other properly, the best tolerability. It's approved for all children and children of ages, unfortunately have only IV formulation, has a broad activity, as you see there's some weakness with terreus but also, with the fusarium, trichosporon which are anyway hard to treat. And the problem with the amphotericin B is the nephrotoxicity, and also like the rise of creatinine You don't see that often, but more a loss of potassium. Moving on to the broad-spectrum triazoles. You probably know a voriconazole which is now approved for children from two years and older. We have and that's the nice thing here. You may have an IV formulation and an oral formulation. So, you can start like with an IV and move like in an outpatient setting to an oral formulation. The CNS penetration is excellent. So, this is the track of choice when you have, for example, invasive aspergillosis of the CNS. Posaconazole it's approved in the US for children 13-years and older, and unfortunately to date it's not approved in the EU for children and adolescents less than 18 years. You have to know that the first formulation was a solution, but then, we found out that the blood level is not sufficient in children. Somehow, they don't resolve it that well. Now they have for adults also these low-release tablets. And this release tablet and if you crush it, then you can dissolve it. This is a new formulation. They tested it now in children, as well as they did with the IV formulation. So, these slow-release tablets also in the solution gave us really sufficient level. And I would always try to use these, and we have these 100-milligram tablets. Usually, you can use those, in those... at least for those who are 13-years and older. It has an activity which is similar to voriconazole but and this is very important and it's a huge advantage. It also includes micromycetes. The problem with the triazoles is that they have multiple drug-drug interactions, for

example, with vincristine, cyclosporin. So, if you want to give it as a prophylaxis in ALL for example, then, we have the problem, how we do it, especially in the induction when we give a lot of vincristine. And for those, especially for the voriconazole therapeutic drug monitoring, the TDM is strongly recommended. We have, for example, one patient right now on our ward who has an aspergillosis, we started with voriconazole, but at the same time with AmBisome because the voriconazole every wants to measure it after two or three days, was not sufficient. So, then you lose really very important time that you have a sufficient blood level to treat the infection. The echinocandins, we have caspo, mica and anidulafungin there approved for children of all ages. Unfortunately, again, we only have an IV formulation, all have basically the similar activity, you can see here, this is only in-vitro, the parapsilosis, it does not, or it seems not to have really a clinical relevance for our children, and in the cryptococcus and also the zygomycetes they're not covered here. They have an excellent tolerability and no major CNS penetration. So, again, just to remind you, please, ask the question and we will discuss it later on. Coming back to the antifungal strategies. And I would like to talk about the prophylaxis. And these are the ECL eight., ECL is in European Conference of Infection in Leukemia. And they, have since 2014, we published the first ECL four guidelines on antifungals in children. And this was an update now, which came out this year in Lancet Oncology. And the primary antifungal prophylaxis is strongly recommended for pediatric patients. And they were set. And this is the same as for adults, which are at high-risk, like 10% estimated natural incidents of invasive fungal disease. And the natural incidents it's very difficult to find out now new treatment protocols where you usually, or in many of them you prophylax them. So, it's hard to do like a study, looking at the natural incidents of invasive fungal disease. And as I showed you before, these includes patients like with AML, recurrent leukemia, high-risk acute lymphoblastic leukemia, and those undergoing stem cell transplantation. And then, the big question, and this is really hard to answer, what compound should be used? As I said here, posaconazole, I think this is a very nice compound in the patients aged 13-years and older. And this has been proven really to reduce mortality in adults with AML and also with chronic mGVHD. So, these data are transferred and they have a strong recommendation. Itraconazole you can use it, but this is not that well-tolerated in many of those patients. But again, these azoles, we have problems with this drug-drug interactions. So, you have to be very careful. Then, these are data also from children, liposomal amphotericin B, which is not approved for this indication I have to say, it's approved for children. So, there are different dosing schedules, either you give 1-mg/kg every other day intravenously, or 2.5-mg/kg twice per week intravenously. These data are more like historic data. So, we don't have a randomized comparison whether it's really effective. But for example, we in our hospital, use this schedule here. Voriconazole is approved for this indication. It has a quite complex dosing schedule. I don't show you here. But again, as an aid with an azole, it's sometimes very complicated to find really the time-period when you can administer. Micafungin, also, it's approved here for prophylaxis, actually, of candida infection and neutropenic patients with this dose be used also here, 4-mg/kg twice weekly, because it has a linear PK-PD, so, it works. But again, I mean, these data are quite weak. I have to admit because we never really randomized or prospectively evaluated the efficacy. Caspofungin, this did not get any rating here because when we did these guidelines, the study by Brian Fisher, which was published in Jama and he compared to caspofungin verses voriconazole or nothing in AML patients and found that this was or showed a significant efficacy, was not out at that time-point. I think one can use it also. It's like the micafungin, but again, here, we have to have a daily infusion, and this is cumbersome for many of those patients. Moving-on to the empirical therapy. And this is a long standard of care in patients who are neutropenic for a long time, ANC less than 500 for at least 10 days. And they have persistent fever for more than three to five days, which is resistant to broad-spectrum antibiotics, or they have recurrent fever despite these broad-spectrum antibiotics. This is showed here, fever refractory to antibiotic in neutropenic patients. And you can see it from two different angles. Either you can say it's a targeted prevention in high-risk situation, or it's an early treatment of acute infections. And there were four prospective randomized trials in children. I don't go through all of them, but what they did, basically, they evaluated amphotericin B deoxycholate against two different dosages of AmBisome, then conventional ampho B against ABCD, the lipid formulation of ampho B. Then, caspo versus AmBisome. And here also, it is Italian study in high-risk children and they included no-treatment in 47 low-

risk children. And these are the guidelines and there are different guidelines, also here, one from a panel published both in JCO, 2017. And you can see all of us agreed that caspofungin and liposomal amphotericin B they have an AI recommendation, because they, also, they are both approved for this indication in children. And we have similar safety and efficacy data in really large adult clinical trials. And in patients who receive a mold-active antifungal prophylaxis, it makes even, we don't have the data, but it's rational to switch to a different class of mold-active antifungals, meaning like if you give liposomal amphotericin B for example, in these children as prophylaxis, you should switch to caspo and vice versa. The pre-emptive treatment, we do not have that many data. What the pre-emptive treatment tries to do is to narrow and to this population who receives antifungal treatment, as you can see here, we have here as an... like an indication for treatment, fever refractory to antibiotics, but here, as fever refractory to antibiotics plus antigen positivity and/or pulmonary infiltrates. And there were only for a long time, adult data, but Maria Santolaya in Chile published, in 2018, a very nice study, where she randomized children, 149 children, for empirical or pre-emptive therapy. And what you can see here, except for the days of antifungal, here you see, here 11 versus 6, it's highly insignificant. There was no major difference between empirical and pre-emptive arm, meaning there was no difference in mortality and also the days of fever, days of hospitalization and so on but the down part is in this that you have as preconditions for pre-emptive therapy, you have to have a galactomannan assay with a quick turnaround. For example, you should have it daily. And we in here in a big university hospital, for example, the microbiology just assesses the galactomannan only twice weekly. Also, you have to have a CT scan available daily. And just to go and move on a little bit on this diagnostic, for example, the galactomannan, it's a cell wall antigen of Aspergillus species. And the test usually, I mean, it has a high negative, higher negative predictive value, but a low positive predictive value. We have causes of false-positivities, we have to really to have in mind, if you do it in a patient where you really don't think he's at a risk for invasive fungal disease, and it comes back. So, don't start antifungals And, because we have like the cross-reaction from existing non-Aspergillus fungal infection, the intravenous administration of some beta-lactam antibiotics, and also very various blood products. But we also have false negative results. And in particular, in patients receiving mold-active prophylaxis, and therefore, the guidelines they recommend, if you want to do galactomannan screening like twice or three times a week in neutropenic patients, you can do this, but discourage this strategy in those patients who receive mold-active prophylaxis. And galactomannan, you can assess in blood and that's a normal thing, but you also can... and there is more sensitive, you can assess this in broncho-alveolar lavage, and also where it's not, that's what I think it's not approved, but we recommended in CNS, if you have the suspicion of an CNS invasive aspergillosis. And the diagnostic use also is in children with prolonged febrile neutropenia and abnormalities in the chest CT, really would do as much as you can do for diagnostics. And just moving to the pulmonary CT scans in adults. We know the systematic CT scans allow earlier diagnosis of invasive pulmonary aspergillosis which is associated with improved prognosis. For sure, we cannot do the systematic CT scans in children. And in adults, the pulmonary nodules, in particular, the nodules with halo sign, air crescent sign and cavitation are typical CT findings for fungal pneumonia in adults. And the appearance of these findings depends on time of imaging and are not specific for fungal infection so, the halo sign, it's an early sign, and then, it usually disappears and you have an air crescent sign or cavitation. And the data, unfortunately of typical CT findings in children are scarce and contradicting. Just to give you a potential algorithm in what you could or should do in febrile neutropenic children with lung infiltrates who have febrile neutropenic child with a lung infiltrate, for sure, you should continue, add or modify the antifungal regimen, which depends on the prophylaxis or on the empiric therapy. And then, you should think about the diagnostics regarding IFD. I definitely would do the GM in blood then, I would talk to the radiologist, pulmonologist, if could we do a BAL and/or a biopsy of this infiltrate. And then, I would do everything I have in hand, I would do a microscopy of this culture. And I would look for the BAL, the GM and also, would do a PCR. And if I have, and this is, you know, in the guidelines, if I have pulmonary, proven probable pulmonary aspergillosis, I would definitely do a CNS imaging, and an MRI of the head, because what we know from small studies that about one third of the children, they are asymptomatic despite they have CNS invasive mold infection. Then, moving-on, and this is the last part to

the specific therapy. I just show you just briefly before we can discuss all the things. The guidelines say, if you have invasive candidiasis in neutropenic patients, then, you have this A recommendation for either caspofungin, micafungin and the liposomal amphotericin B as well as a single dose, 3-mg/kg per day. And then, invasive aspergillosis, as I said, if voriconazole with an... I show you here, this is this dosing schedule, which is quite complicated. Less well-rated is the liposomal amphotericin B, but again, it's problematic sometimes to receive or to get a sufficient serum level. So, what we often do in those patients where we know it's an invasive aspergillosis. We start with both and once we have the sufficient level, then, we stop liposomal amphotericin B. All these others, they do not have a really high rating. The isavuconazole, it does quite well in adults but we do not know really that much in the pediatric populations today. And just last, the mucormycosis, which is very difficult to treat. Here you should use the liposomal amphotericin B with a single dose, at least 5-milligrams. And the combination therapy could be plus caspofungin, plus posaconazole. And to be honest, but we do usually use liposomal amphotericin B plus posaconazole, but don't forget all these other things that you should, we'd use in those, for example, with GVHD immunosuppression, you might use the hematopoietic growth factors, and it's very controversial, whether you should give in those neutropenic patients, granulocytes transfusion. For example, it has been shown in a retrospective study that it might be even associated with a worse outcome in pulmonary aspergillosis, which we don't do it as either but if you have some other sides, it might be beneficial. And especially in mucormycosis just consider at a very early time-point the surgery, which also has an important place, a very important role in this fungal infection. Just to show you your take-home messages. So, IFD is associated with a significant morbidity and mortality. Diagnostics, GM and CT, but consider also BAL and biopsy. To prevent, it's problematic, especially in ALL, which is a very heterogeneous group. And we have to learn, and this we are trying to do, to identify patients who benefit from prophylaxis. It's not really feasible to run a randomized trial on that. It's very difficult for a lot of patients, which antifungal compound should be used. Empirical antifungal therapy in most standards of care with AmBisome and caspo. Pre-emptive antifungal therapy, we have little data. And the preconditioning, again, is the rapid availability of GM and the CT scan. And the specific therapy you should and this is what I also do have a look to the pediatric specific guidelines. With this, I am at the end. I thank you, I'm ready for the discussion, which hopefully... it won't go that badly as shown here. And again, please send your questions and comments. Thank you very much. So, I think there no questions at the moment. I really can encourage you. Or maybe it was really that clear what I presented or is that easy? And there are no questions. I can tell you one thing where we really look at the moment. I mean, it's very complicated. We have like one osteosarcoma patient who has a hypothesis right now, and he has a skin infection with Aspergillus, which makes us really unhappy because it might be that we have to amputate the leg. So, we treat him with at the moment, also with AmBisome and voriconazole, just to prevent the spreading of this infection. So, there it's not only the pulmonary or the CNS infection with the Aspergillus, but you can have it also on different sites. And that makes it much, much more complicated. So, we wait, I think another minute or two for questions, but you really feel free. And otherwise, I wish you a nice evening and thank you for attending. So, I think now we can close the session. So, everybody has a good night and I hope to see you soon. Thank you very much.