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Febrile neutropenia in paediatric cancer patients

Prof Simon: Hello and good evening. This is Arne Simon, from Homburg in Germany, and it's really a pleasure for me to discuss with you about antibiotic stewardship in pediatric oncology. I decided not to speak about the basics of the febrile neutropenia, because I suppose that most of you are pediatric oncologists, and so this is your daily task. And so, I would like to focus on targets of antibiotic stewardship. Is it possible to perform antibiotic stewardship in pediatric oncology and is less-more in this topic? I'm from Germany, and I'm one of the coordinators of the German Recommendation concerning febrile neutropenia diagnostics and treatment in pediatric cancer patients, and we have a Commission for Hospital Hygiene and Infection Control in Germany which is allocated at the Robert Koch Institute and this commission recommended in 2020, that internal guidelines for antimicrobial stewardship in clinical settings specialized in the treatment of immunodeficient or immunocompromised patients should be adjusted to particular issues relevant in this heterogeneous patient population. And the main challenge for the attending oncologists and hematologists, infectious disease specialists and ABS teams is to identify critical targets for antimicrobial stewardship and antifungal stewardship and to translate the resulting interventions sustainably into clinical practice. We're currently re-evaluating our German guideline and we are going to focus much more on antibiotic stewardship topics. The first example is if you have a patient who is admitted to the hospital with a newly diagnosed leukemia, as Monica Khurana described in this study, and this is very interesting because many of those patients have fever, 67% of all patients with neutropenia in these situations, and about half of all patients with normal granulocyte counts, but positive blood cultures were only found in 1.6%. This is the first target ABS conclusion. In pediatric patients with newly diagnosed ALL and fever, please perform an in-depth search for a serious bacterial infection, including blood culture where clinical applicable, a urine and stool cultures and viral PCRs from respiratory samples and an x-ray of the chest. And in case of negative blood cultures and clinical response to the empirical antibiotic therapy, it is possible to consider cessation of this therapy after three days irrespective of neutrophils counts. Some years ago, we performed a survey in 51 pediatric cancer centers in Germany, Austria, and Switzerland. I'll show you some slides which derived from this paper, and this is one concerning the first-line antibiotic therapy in febrile neutropenia in these centers. What you can see here is that 60% use piperacillin-tazobactam as first-line treatment, at about a quarter uses ceftazidime, some use cefepime, and our colleagues from Switzerland typically use ceftriaxone and amikacin, where amikacin broadens the spectrum of ceftriaxone to *Pseudomonas aeruginosa*. But there are still 6% of all the centers which use imipenem/cilastatin or meropenem as first-line treatment in febrile neutropenia without a focus. If you look at these numbers, we can first speculate that using a broad-spectrum cephalosporins from group IIIB or from group IV as first-line treatment may increase the selective pressure on multidrug-resistant Gram-negative pathogens and viridans group streptococci. Cefepime is an adequate alternative in patients with piperacillin tazobactam-related adverse drug reactions. Some of our patients develop exanthema after Pip-Taz administration or prolonged neutropenia, or first-time neutropenia, I've seen this for example in Hodgkin's patients. But what is very important from our perspective is that meropenem or

imipenem/cilastatin as first-line treatment should only be considered in patients who are colonized with multidrug-resistant Gram-negative pathogens and in all patients with clinical signs of sepsis, but these patients do not belong to the group of fever without a source. From the same publication, I can show you here, the distribution of empirical monotherapy which is implemented only in 42% of all these POCs, Pediatric Oncology Centers, and we divided these centers into small, large, and medium sized centers. And interestingly, the proportion of centers using combination therapy was greater in small centers than in the big, large centers.

In which patients with fever without a source and neutropenia pediatric cancer patients, first-line combination therapy should be considered? This is a very controversial issue because we have some very good meta-analyses, which led to the conclusion that combination therapy is no better than monotherapy. Nonetheless, pediatric oncologists seem to be reluctant to use monotherapy in certain patients and these are some examples. For example, patients with acute lymphoblastic leukemia, prolonged neutropenia for more than 10 days, and high-dose steroids, this is a case in some patients with ALL induction treatment; patients with after high-risk cycles, and patients with relapsed leukemia. Those patients who come in and have a transient low mean arterial blood pressure, which responds to a volume bolus without the need for catecholamines, and patients with an increased risk of bacterial translocation. For example, with severe mucositis, or perianal skin or soft tissue lesions. Thomas Lehrnbecher has shown many years ago that these perianal soft tissue lesions put the patients at an increased risk of *Pseudomonas aeruginosa* bacteremia. Some pediatric oncology patients may decide to use combination therapy, if they have higher resistance rates of the Gram-negatives against Pip-Taz, for example, more than 20% of all blood culture isolates displaying this resistance pattern.

The first-line combination therapy with a glycopeptide should be considered in patients with leukemia, in particular, AML after high-dose cytarabine and in patients with skin and soft tissue infections, for example, allocated to the long-term central venous access catheter, Broviac, Hickman, or Port type, and it should be considered in patients with previously known MRSA colonization.

In the last years, there have been some discussions concerning potential harms, which may be brought to the patients by using combination therapy. This is an outstanding study from Gab Haeusler and her team from Australia which prospectively documented 848 events of febrile neutropenia in 462 children and adolescents. Aminoglycosides were used as combination treatment in about 30% of all events. What the investigators realized is that there was a very low adherence to national guidelines concerning the decision for, or against the use of these agents. They asked whether there was any measurable effect of aminoglycoside combination treatment during the first 12 hours. In multivariate adjusted analysis, they revealed a significant higher risk for adverse outcomes in patients with combination treatment. From the other side, there was no increased risk of an unfavorable outcome in patients being eligible for combination treatment (according to the guideline) but did not receive aminoglycosides. At the end of the day, we should, again, critically consider when this combination treatment is necessary.

If we use aminoglycoside we should, in my opinion, use it wisely and perform a drug monitoring. If you look at gentamicin, for example, we have defined the standard dose of this substance by body surface area. The reason for that is that gentamicin elimination is heavily influenced by the age of the patient in patients with normal or with augmented renal clearance. These doses are much higher than the doses you can find in the package insert. It is administered as once-daily infusion because the critical PKPD target is the maximum concentration (Cmax), which should be for example, above 10 mg/L. In addition, you use the through level (or sampling after 8 to 10 hours) to confirm that the drug is readily eliminated from the body. So, from our own studies and from studies of others, we can conclude that if you use gentamicin or tobramycin in the first 72 hours of the febrile event, use single-day dosing and perform drug monitoring and adjust it to the renal function, there seems to be no genuine oto- or nephrotoxicity in pediatric cancer patients.

It still remains important to consider contraindications for aminoglycosides such as pre-existing inner ear ototoxicity, for example, in patients with platin treatment, neuroblastoma, severe neuropathy e.g. due to vincristine alkaloids and pre-existing renal impairment including chemotherapy induced Fanconi syndrome, because nephrotoxicity of aminoglycosides does not only refer to an increase in serum creatine and decrease in creatinine clearance, but also to Fanconi syndrome-like adverse events.

In this study from Stephanie Hennig, the team decided to change their regimen to a preferred monotherapy with Pip-Taz. Interestingly, the proportion of antibiotic cycles with combination therapy decreased from about 80% to 21%. And this is quite near the proportion of patients who receive aminoglycoside in our department, less than 20% and the proportion of aminoglycoside cycles without therapeutic drug monitoring decreased from 44% to 0%. The empiric first-line combination therapy with aminoglycosides should be regularly discontinued after 72 hours in clinically stable patients with negative blood cultures or blood culture results, which allows a targeted monotherapy. Many pathogens do not need combination treatment.

And the same case, we see glycopeptides. I know from a recent study, which we have done in many cancer centers in Germany, that if this cancer center starts vancomycin or teicoplanin, it is not considered to discontinue it after 72 hours, and so, the patients receive it as long as they have fever or as long as the antibiotics are administered. And this is not very reasonable because glycopeptides are definitely used to treat methicillin-resistant gram-positive pathogens or viridans group streptococci. And so, this combination treatment should critically be reevaluated after 72 hours, and then it can be discontinued in most patients. We have restricted the use of glycopeptides in a former study which has been performed in Bonn in the center of UKB. What we reached was a sustained reduction of teicoplanin use up to 90%. Fosfomycin may be used alternatively to glycopeptides in patients with persistent fever for longer than 72 hours if you want to broaden the spectrum to Gram-positive and other Gram-negative pathogens, and this is a standard dosing of this antibiotic (150-300 mg/kg/day in three divided doses).

There is much debate about the most appropriate dosing of vancomycin in pediatric oncology patients. In one study from Hilary Orr from Houston, Texas, they started with 60 milligram per kilogram per day, which is higher than the dose, which you can find in many textbooks (40 milligrams per kilogram, per day). They defined the target therapeutic concentration between 10 and 20 mg/L. Only 12 patients (21%) achieved this target concentration, while the others mainly had trough levels below 10 mg/L despite the fact that some of them received additional nephrotoxic agents, such as furosemide. And so, our conclusion is first that in children with normal or augmented renal clearance, the vancomycin starting doses should be 60 milligrams per kilogram per day, at least. The most appropriate through levels in children (sampled before the third vancomycin dose) are still controversial. From adult studies, including patients with MRSA bacteremia or MRSA pneumonia, we know that it is reasonable to reach an AUC/MIC ratio above 400. This refers to MRSA isolates with a minimal inhibitory concentration of below 1.5 mg/L. Interestingly, in a study from Andrea Hahn, investigating clinical outcomes of pediatric patients with MRSA bacteremia different outcomes did not correlate with an AUC/MIC ratio above 400. The same group and others have shown that in pediatric patients below the age of 10, a trough level of 5 to 10 mg/L may correlate with AUC/MIC ratio above 400. The only significant observation from Hilary Orr's study was that those patients who reached this trough level and received higher doses of vancomycin for long periods had a significantly increased risk of renal toxicity, acute kidney injury. The discussion about the other glycopeptide, teicoplanin is even more complicated because the data concerning the pharmacokinetics in pediatric cancer patients are still scarce. There is a very interesting study from Zhao from 2015, including 84 pediatric cancer patients with the standard dosing of 10 mg/kg, three times every 12 hours and then once daily. The authors define the trough level above 10 mg/L as adequate and 48% of the patients remained below this trough level. If you look here at the different age groups, you can see that children need at least 18 milligrams per kilo per day, to reach this trough level above 10 mg/L in 50 of 100 patients. This starts the discussion if it's necessary to give a higher Teicoplanin maintenance dose.

The therapeutic target is not as well defined in vancomycin, but in practice, when we use Teicoplanin for in patients with a severe infection due to a Gram-positive methicillin-resistant pathogen, we increase the dose, because it's allowed to use daily doses up to 800-milligram of this substance.

An additional problem concerning the use of vancomycin is that its combination with Piperacillin-Tazobactam definitely increases the risk of acute kidney injury. This is not only the case in pediatric intensive care patients, but it's also the case in pediatric oncology patients. In one study, the incidence of acute kidney injury was 27% versus 7% in those with a Vanco-Pip/Taz combination therapy. In addition, the latency from the start of the antibiotics to acute kidney injury was shorter in the Vanco-Pip/Taz group, and in patients Vanco trough levels above 20 mg/L.

When should the therapy be escalated? From the survey of Max Scheler, almost half of all 51 POCs who participate in this survey escalate the antibiotic treatment in a patient with febrile neutropenia after 48 hours. The corresponding German guideline recommends to escalate after 72 hours. The last version of the German guideline and the international guideline outline that persistent fever alone without any change in the clinical appearance and condition is no mandatory reason to escalate antibiotics if you have negative cultures and no clinical focus. This applies in particular to patients in whom the white blood cell count is expected to recover during the next days. You can leave the patients on first–line antibiotics and wait until the neutrophils recover.

What is the minimal duration of intravenous treatment? Surely this depends on the local situation concerning the availability of outpatient cancer treatment or nursing services. And you can see here that concerning the 51 centers in Max Scheler's survey, one quarter stated that they may stop IV treatment after 48 hours, others use 72 hours and some use longer periods. The conclusion from the target ABS perspective is that it is possible to stop IV antibiotics after 72 hours in clinically stable, low-risk patients without fever for at least 24 hours irrespective of the neutrophil count. You don't have to wait for an increase in the neutrophils and this patient can leave the hospital on the same day, unless no other reason necessitates the inpatient treatment. In some locations, this may be different because they have very long distances to drive until they reach the pediatric oncology center but this is our practice since many years. 42% of the POCs advice against this conclusion and wait with the cessation of antibiotics until they observe definitive signs of neutrophil recovery.

One important and perhaps "low-hanging fruit" concerning antibody stewardship in pediatric cancer patients is the **peri-operative antibiotic prophylaxis**. In a study from Genova, the group of Elio Castagnola performed a retrospective analysis and evaluated the incidence of surgical site infections after tumor operations in pediatric cancer patients using of a small spectrum cephalosporin (cefazoline) 30 minutes before the operation, plus two additional doses in 24 hours. In many operations, it would not be necessary to add a second or third dose but many tumor operations last longer than four to six hours and the patients are immunocompromised so, I think this may be reasonable, but the most important result is that they did not observe surgical site infections. Also, the spectrum of this antibiotic mainly covers a staphylococci, for example staphylococcus aureus, which is by the most important pathogen concerning or causing surgical site infections. And so, from the perspective of ABS, antibiotic stewardship, reconsider your institutional practice for perioperative antibiotic prophylaxis, do not use broad-spectrum antibiotic, and do not administer any perioperative prophylaxis for more than 24 hours.

A very controversial issue in this context whether if it is possible and safe to deescalate the intravenous antibiotic treatment if you still have a neutropenic patient with a defined pathogen in blood cultures for which the in vitro sensitivity is known. In a recent study by James Reinecke, there were 67 patients with ALL and AML. At the end of the day, it was possible to deescalate a) in 25 of 36 patients with positive blood cultures and b) in 19 of these 25 on clinical grounds. Eventually, a de-escalation to an antibiotic treatment with a smaller spectrum of activity was performed in 9 of 19 (47%). This deescalation had no negative impact

on outcome. This is something we should discuss further and evaluate in prospective clinical studies, since de-escalation is a very important instrument of antibiotic stewardship.

If you want to talk about antibiotic stewardship, you have to evaluate the antibiotic consumption in your unit, and that's what we have done. In a recent publication by Svenja Ockfen, we included 235 consecutive pediatric cancer patients and investigated the use of meropenem in our patients. 19% of our patients received at least one cycle of meropenem in 57 febrile neutropenia events. Interestingly, only 5% of these patients were colonized with multidrug-resistant gram-negative pathogens, which is one reason to use meropenem in febrile neutropenia. In 8.8%, the blood cultures yielded a gram-negative pathogen. Concerning definite treatment, there were appropriate alternatives to meropenem which a smaller spectrum of activity in 4 cases, but de-escalation was not performed. So, if pediatric oncologists use meropenem, they are reluctant to stop meropenem and to deescalate to a smaller spectrum antibiotic. The median length of therapy in the meropenem group was 6 days, and the corresponding median days of therapy were 12 days. Days of therapy count each antibiotic which are administered on a definite day. So, if you use meropenem and teicoplanin on one day, this refers to two days of therapy and this higher value for days of therapy shows that meropenem is used in combination in at about a half of all events. If you look at the data which we can derive from pharmacy dispensing, we see how much is the amount of meropenem delivered to the pediatric oncology ward per month or per quarter. This study revealed that meropenem consumption according to pharmacy dispensing data was 1.95 times higher than the patient-derived real consumption. So, it seems not reasonable to use pharmacy antibiotic dispensing-data as measurement for real consumption, as long as the antibiotics are not prepared in the pharmacy, but on the ward.

One very important aspect of antibiotic stewardship is infection prevention. I just want to remind you that there are very feasible, and beneficial preventive bundles concerning the use of long-term intravenous catheters such as Broviac, Hickman or ports. It is possible to avoid many of the infections which are related to the use of these devices. We published a modified Broviac maintenance bundle (Furtwaengler et al.) and could confirm that the introduction of this bundle led to a sustained reduction in particular of gram-positive bloodstream infections due to Coagulase-negative Staphylococci. We have national recommendations concerning evidence-based maintenance care for these devices from the German Society of Pediatric Oncology and Hematology.

Let me add very few information on antifungal treatment. This is a very separate issue, but one important thing is that the addition of empirical antifungal treatment should be considered in certain patients, with a high-risk for an invasive fungal infection after 96 hours of persistent fever. If you look yet at this distribution, in Max Scheler's survey, 40% add a systemic antifungal, such as liposomal Amphotericin B or Caspofungin after 72 hours. Patients who do not have a high risk or clinical signs of an invasive fungal infection, and perhaps a negative Plataelia™ antigen in serum do not need these antifungals. We investigated the use of systemic antifungals in our center too (Sauter et al.): The proportion of those receiving at least one cycle of systemic antifungal treatment was the same as meropenem. In high-risk patients antifungal prophylaxis relies on micafungin or liposomal amphotericin B two times a week administered in our outpatient clinic. We use Caspofungin or liposomal amphotericin B as empirical treatment in high-risk patients with fever, which persists for longer than 96 hours. Following this schedule, we have not seen any mortality related to invasive fungal infection during the observation period, but we do not treat patients with allergenic transplantation during the acute phase. We start treating these patients for example after 40 days.

There are some barriers and goals in pediatric oncology concerning antibiotic stewardship. There is a study from Joshua Wolf (Boston). He asked 97 pediatric cancer physicians and infectious disease physicians "What are the main goals of antimicrobial stewardship in pediatric oncology?". Predominant goals were to reduce the time to de-escalation, to avoid the initiation of unnecessary antibiotics, and to reduce redundant coverage. One example for this is if you use metronidazole plus Pip/Taz, because there's no need to use metronidazole, in the patient receive Pip/Taz. Unfortunately, this study revealed some important barriers for

antibiotic stewardship in pediatric oncology. They are first related to missing resources, insufficient data analysis, and insufficient clinical time to discuss antimicrobial stewardship issues. The antimicrobial stewards, infectious disease specialists do not have enough power or authority to influence the schedule on the ward, but in addition, there are some barriers related to the oncology clinicians. For example, they are more motivated by fear. Somebody has allocated antibiotics to the “drugs of fear”. They are fearing rare adverse events and adverse outcomes related to the infection. They don't realize that the uncritical use of antibiotics may cause adverse outcomes too. Many pediatric oncologists are very confident to their traditional schedules and it is very difficult to implement a sustainable change concerning this antibiotics' practice. Some treatment protocols for example, derived in our case from the German Society of Pediatric Oncology and Haematology in Germany, are not very constructive concerning these issues because they do not include many aspects of prudent use of antibiotics. They always err on the side of caution.

Let me present you finally a small case, a 6-year-old boy with a neurogenic bladder dysfunction because of spinal metastases of medulloblastoma. He has suprapubic, urinary catheter and a urine culture yielded Pseudomonas species with more than 10^5 colony forming units per milliliter. He has just finished a chemo cycle. So, a decline in his neutrophils is expected and there's a high probability that he will come back with fever. Here you can see the in vitro sensitivity of this bacterium referring to the EUCAST systematic. The isolated species is *Pseudomonas corrugata*, and interestingly, *Pseudomonas corrugata* is a plant pathogen, it causes tomato pith necrosis. From my knowledge, it has never been described as a pathogen in humans. Accordingly, we decided not to treat this patient despite of the high colony forming units and the colonization with this plant pathogen disappeared spontaneously.

Prof Lehrnbecher: I also would like to thank you, Arne, was an excellent talk and I have a look now, there is no questions in the chat right now. So, please, now, you still have the opportunity to ask some questions. In the meanwhile, I would like to ask you, what would you do, for example, with AML patients who are expected to having period of neutropenia of let's say, 20 to 25 days, first having like fever, you did not find any pathogen, but you escalated because the patient was doing worse. So, at the end, you, maybe you have meropenem. If the patient stopped, there's no more fever after let's say 10 days, would you deescalate like to Pip/Taz or you would stop antibiotic therapy? What would you do?

Prof Simon: First of all, it is important to look at the clinical situation concerning where in the protocol the patient stands. In our pediatric oncology center, AML patients stay in the hospital after the first induction course, and they stay in the hospital until they recover clinically. After neutrophil recovery, they are sent home, for example, for two or four days and come back for the next induction cycle. In this situation, I would prefer to stop the antibiotic after 48 hours if the patient is in a good condition and has negative cultures, because he is constantly on clinical observation. But for example, I would most probably not stop the antibiotics after 72 hours if the patient has started fever three days ago, and he's expected to have neutropenia for more than 20 days afterwards, then, I probably would stay on Pip/Taz and wait at least two or three days and decide on clinical grounds. Many of these patients have severe mucositis and this may be one reason to continue antibiotics because we use in these patients not only morphine and infusion, but we use metamizole as analgesic. In this situation, it may be difficult to identify patients with fever.

Prof Lehrnbecher: So, I mean, we do more or less the same, but I think it's always hard to read, to decide whether you deescalate, you stop, because many people say like, you never change a winning team. And so, you continue kill the neutrophils count really increases and this has been the guidelines some years ago, but now, I think more and more people are relaxed. I mean, that's also the other question. I mean, to dismiss the patient, I mean, there was one paper by Lillian Sung who showed that the only difference between early dismission or keeping exactly those AML patients in the hospital is just that they had a higher incidence of C-Diff, but the morbidity mortality was exactly the same, but it's different. And I think it's also very important to see the local circumstances, whether they have a positivity, to come in, like...

Prof Simon: Unfortunately, we do not have such a service for our patients. We have an outpatient clinic, but we have no healthcare workers / qualified nurses who can go at home to the patient, for example. I think this is a question concerning the insurance of the patient too. I suppose that in the US the outpatient parenteral antibiotic treatment has been invented to avoid the high-cost of inpatient treatment. And this is not the same in Germany. The cost is always covered by the patients' insurance.

Prof Lehrnbecher: You're right. So, we are almost running over time, I would like to ask you one short question with a short answer, and then, we have to stop this interesting session. What do you think about, we have now some patients exactly with this prolonged neutropenia, we send them home, but they unfortunately have, which is very unusual in Germany, but they have like to drive one hour, one hour and a half, would you give them, for example, what the Swedish do, levofloxacin and then once they develop fever, they take one of... one antibiotic, and then they go to the hospital?

Prof Simon: No, we would not do this. In patients who have such a long distance to come, we always are searching for contact with the next children's hospital. Patients/Caregivers are advised to go to the next children's hospital, which is normally one in a half hour distance from the patients' home. The adjacent hospital has instructions to contact our pediatric oncology consultant. And we discuss the clinical issues with this hospital. And then, we decide whether they can come to us.

Prof Lehrnbecher: There's one more question came up and we are already overtime on it. Sorry, to interrupt you. You're the gear doctor. Thank you very much for your nice presentation. My question is about stem cell transplantation. If the patient has a fever more than 39 degrees without bloodstream infection, no pathogen probably, probably you do engrafting. Is it indication to start antibiotics?

Prof Simon: Yes, I think it is. The first aim of antibiotic stewardship is to give the patient the best treatment. And there must be no misunderstanding of this. If you have a patient who is in a high-risk situation and the fever, what he displays clinically, may be a sign of severe infection, you can start antibiotics and you can even start broad spectrum antibiotics. The more important thing is to reconsider, for example, after 36 or 48 hours, if this patient really has an infection and you can then decide to stop the antibiotics or to deescalate, if the microbiological culture sampled and at the beginning of the fever event, do not yield any pathogens.

Prof Lehrnbecher: I think this is a very nice summary of the talk, to start early, to hit hard, but then to reconsider, really to stop treatment. I fully agree with you. And with this, I thank everybody who listened, who participated in the talk and in the discussion. And I also thank you, especially, Arne, for this very nice presentation. Thank you very much. And everybody has a nice evening. Thank you.

Prof Simon: Thank you, Thomas, for your assistance.