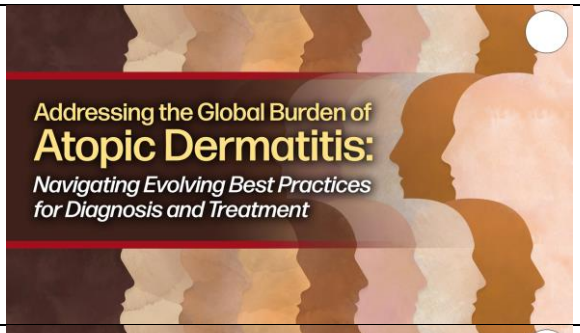
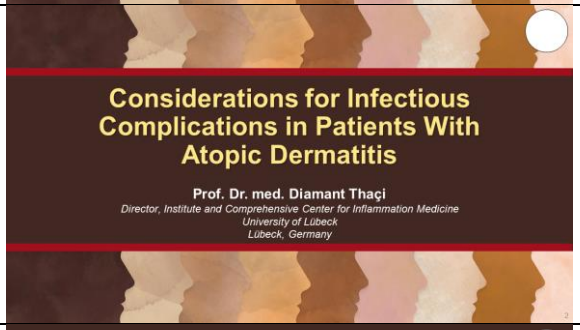
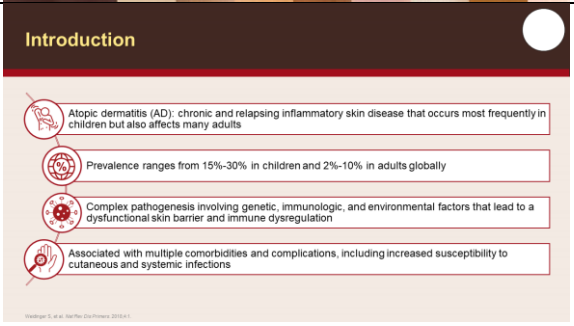
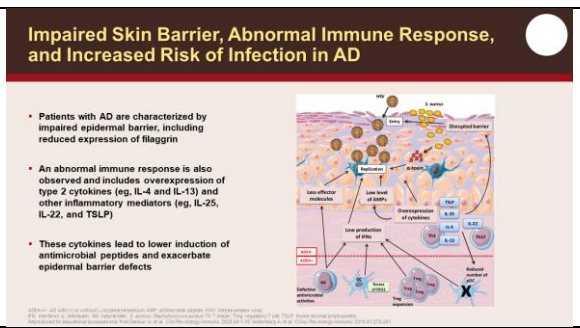
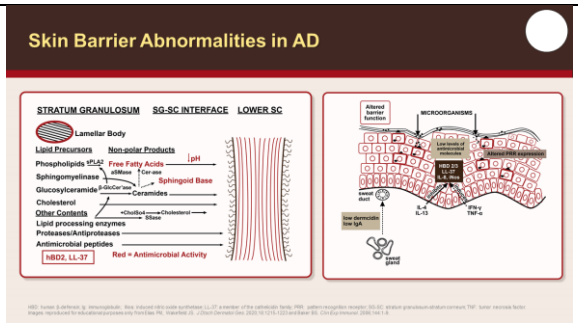
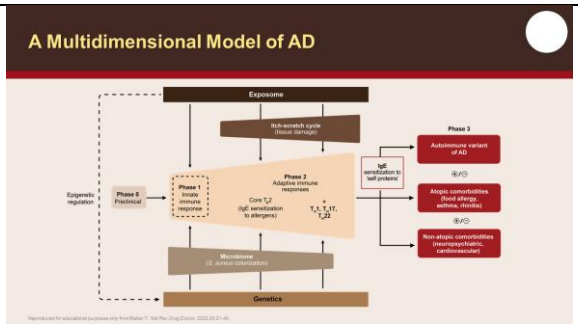
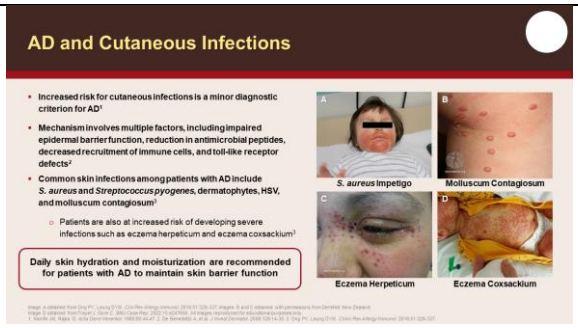
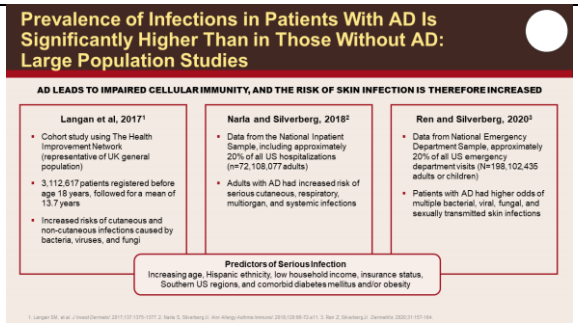
Addressing the Global Burden of Atopic Dermatitis: Navigating Evolving Best Practices for Diagnosis and Treatment

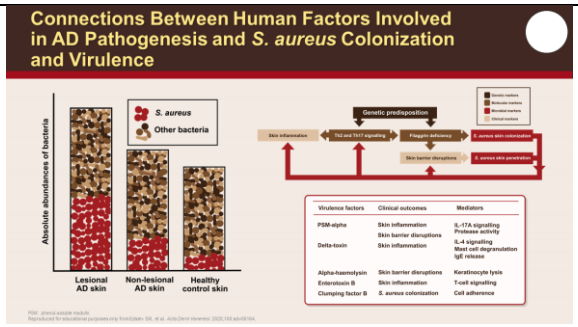
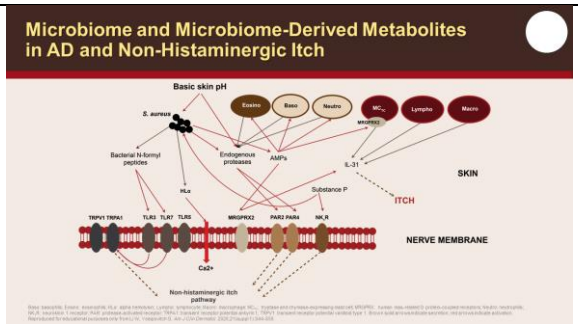
Considerations for Infectious Complications in Patients With Atopic Dermatitis

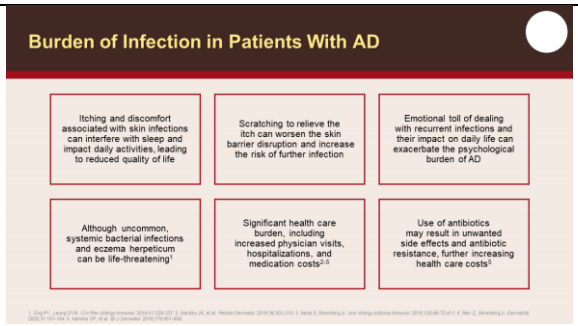
1		Ladies and gentlemen, dear colleagues, it's my pleasure to be part of Addressing the Global Burden of Atopic Dermatitis, as an important tool for us as dermatologists to navigate evolving best practices for diagnosis and treatment.
2		I will consider today and focus more on infectious complications in patients with atopic dermatitis. My name is Diamant Thaçi, I'm a university professor at the Comprehensive Center for Inflammation Medicine at University of Lübeck, in Lübeck, Germany, and I'm very pleased to be here today with you.
3		Let me introduce atopic dermatitis as one of the most common skin diseases that we are facing every day in our daily practice, which affects not only children but also adolescents and also adults. In the past, we thought that mainly children are affected, with a high prevalence between 15% and 30%, and today we know that this is also a frequent disease in adults, where we assume that about 2% to 10% of adults may have atopic dermatitis. It's a complex disease — we agree all about this complexity. It is genetically driven. Immunological factors are playing a very important role. Environmental factors and stimuli are also very important; they are leading to the more immune dysregulation at one part, but at the other side we have also the skin barrier which is impaired. And, of course, the disease is accompanied with itch, which aggravates the signs and symptoms of atopic dermatitis. Finally, atopic dermatitis is also associated with different comorbidities, which may also increase the risk for cutaneous but also systemic infection.
4		Let me start with the first part of my talk, at the beginning of the introduction, showing you the pathophysiology of atopic dermatitis, which is very crucial, as a better understanding of the pathophysiology is leading to a better understanding of the risk for cutaneous and also systemic infection. You might see that in a patient with atopic dermatitis, we

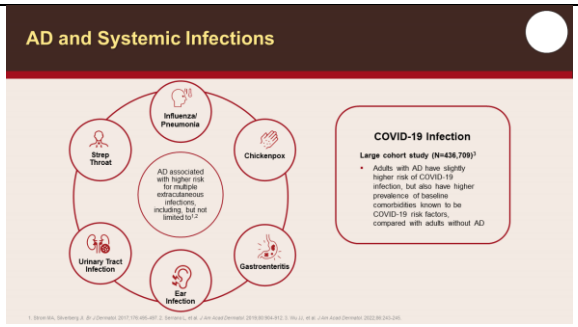
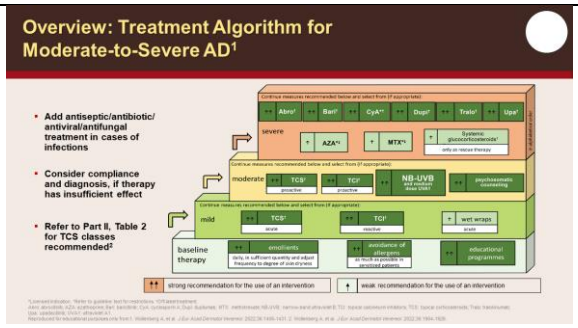
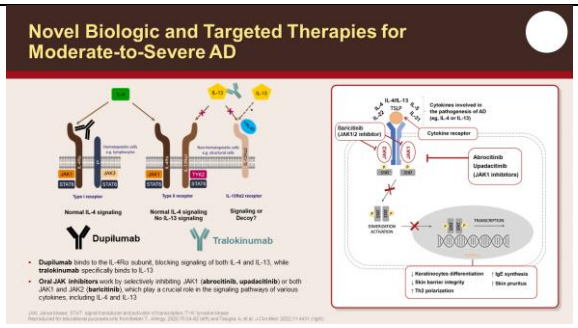
		have type 2 inflammation, at least at the beginning. And this type 2 inflammation in general is leading to the lower production of antimicrobial peptides. A low production of antimicrobial peptides means that the keratinocytes are producing less of these antibiotics of the skin to protect us against different microorganisms, including staphylococci, including also viral infection, which may penetrate easily through the skin of the patient with atopic dermatitis, because as we mentioned at the beginning, it is a disease where we have also impairment of the skin barrier. And if the skin barrier is not working properly, then not only antigens, superantigens, environmental stimuli, whatever, can penetrate easily through the skin, but also viruses, like herpes simplex, or also bacteria, like *Staphylococcus aureus.* And these may interact with the immune system, aggravating the atopic dermatitis at one side, but at the other side also leading to diseases of the skin, cutaneous infection, or even to the systemic infection. And I think this is also particularly important once we are going to the next slide and looking, how is this happening?
5		If you start with the skin barrier, we do agree that the skin barrier in atopic dermatitis is totally different. The abnormalities in the skin barrier, for example, filaggrin mutations, can lead to increased vulnerability of the skin to penetration by microorganisms. Furthermore, certain local factors such as differences in pH, free fatty acids, sphingoid bases, and decreased production of antimicrobial peptides contribute to the increased susceptibility of the skin in patients with atopic dermatitis to microbial penetration. And of course, that what we see here that IL-4 and -13 is inhibiting directly the production of antimicrobial peptides, among them, human beta-defensin 2 and 3, cathelicidin, and also the others. And we see also that the others, for example, type 1 inflammation like interferon-alpha may induce the production of antimicrobial peptide. Therefore, in diseases which are type 1 driven, we have a lot of interferon-gamma, and interferon-gamma protects the skin against the viral infection but also increases the production of antimicrobial peptides,

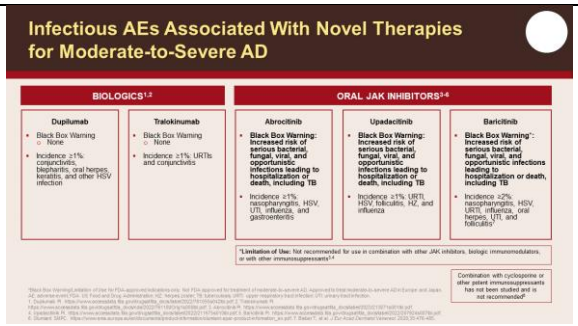
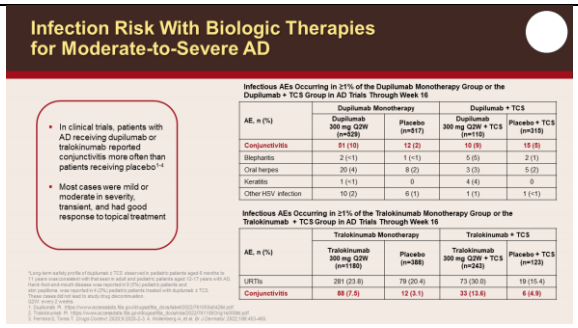
		protecting the skin from infection. And — this is very crucial to understand — the skin barrier in patients with atopic dermatitis is impaired and can lead to more frequent infections.
6		But generally, if you look at the model of atopic dermatitis, we do see that genetics are playing a very important role. But also, the environment is influencing, also, the occurrence of the disease and worsening of the disease. At the very early beginning, we might see that microbiome and especially *Staphylococcus aureus* colonization may drive also the disease, may lead to the aggravation of the disease, and not only simply being something that may cause infection, but something which can also influence the course of the disease. And we do see that in the late phases, or phase 3, we have comorbidities like autoimmune-variant comorbidities, like food allergy, asthma, rhinitis, morbidities like neuropsychiatric, cardiovascular. And all these comorbidities can also increase the risk for infection in patients with atopic dermatitis, especially patients with a moderate-to-severe form of atopic dermatitis.
7		If you look carefully at our patients with atopic dermatitis in daily practice, we do see that patients with atopic dermatitis have increased risk for cutaneous infection. This is even part of the criteria, once we are discussing about the criteria, how to do the diagnosis of atopic dermatitis. There are different mechanisms, as I mentioned. The skin barrier is impaired in patients with atopic dermatitis. Especially in children, we might see a higher increase of risk for viral infection, like for example molluscum contagiosum. And if you see the skin in the patient with atopic dermatitis having molluscum contagiosum, it is not always the inflamed skin. So, it may occur also in the region where we do not really have inflamed skin. Furthermore, the patient with atopic dermatitis has also itch. Itch and scratching is spreading the infection easily from one place to another place. This is more evident in children, but can happen also in adolescents and also in adults, for example, with impetigo. Impetigo is very frequent in children, which is caused by staphylococci,

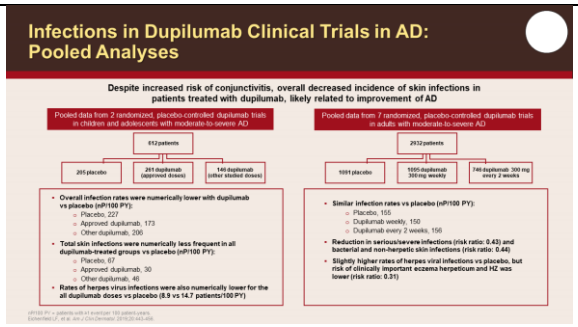
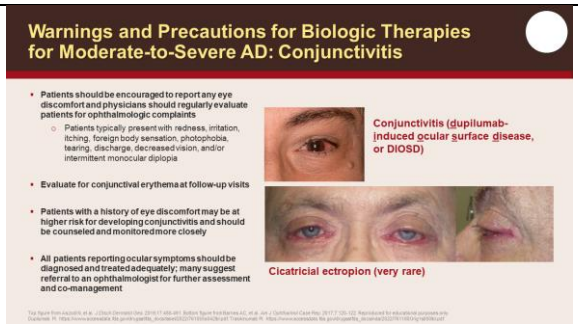
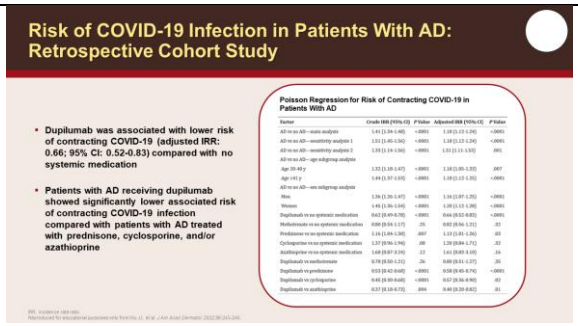
		sometimes also streptococci, sometimes also a mix of both of them, and we see that this is also aggravating the disease. And sometimes it's leading to the need for systemic treatment of children with drugs, which are important to fight the infection in these patients. It is also very important to understand that the patient with atopic dermatitis — children, adolescents, and also adults — may also develop life-threatening diseases like eczema herpeticum, which may occur after a very simple infection with herpes simplex virus. So, I think this is also important. Also, eczema coxsackium can occur in children. So this means that infection in patients with atopic dermatitis can be very mild but also may be life-threatening and very severe, requiring a need for a more intensive treatment. Therefore, it's always very important that we have daily skin hydration and moisturization, that the skin must not be dry because this will aggravate — increase — the risk of infection in patients with atopic dermatitis.
8		Looking at the prevalence of the atopic dermatitis infection, from the different databanks we can realize that the risk of infection is much higher in patients with atopic dermatitis. We have increased risk for noncutaneous infection caused by bacteria virus and also by fungi. A very large dataset from a national inpatient sample study demonstrated that patients with atopic dermatitis are at risk of developing severe cutaneous, respiratory, and systemic infections. Data from national emergency departments have also shown that both adults and children with atopic dermatitis have higher odds of bacterial, viral, fungal, and other skin infections. These findings show the importance of gaining a better understanding of the disease, as well as selecting appropriate and adequate treatment options for these patients. Predictors of serious infection include younger patients (children), but also patients with comorbidities such as diabetes or obesity, or patients with lower socioeconomic status, where we see that infections can occur more frequently.

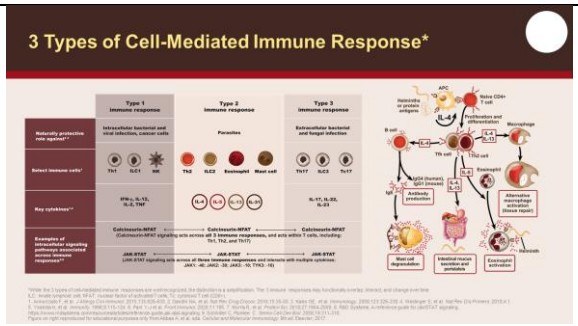
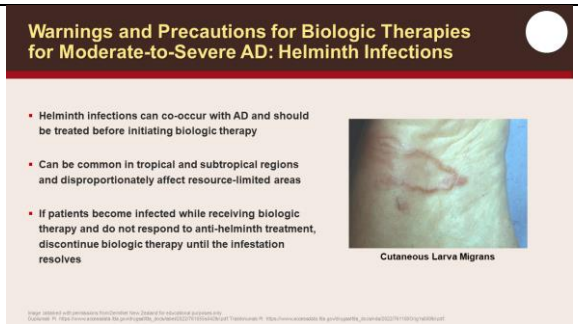
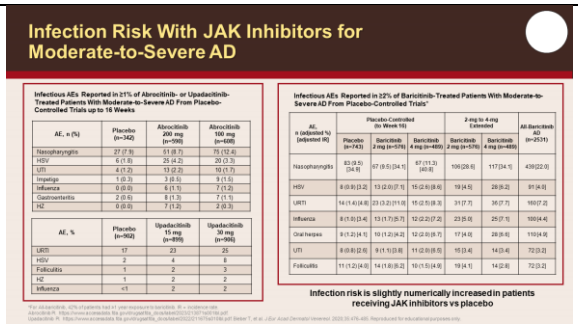
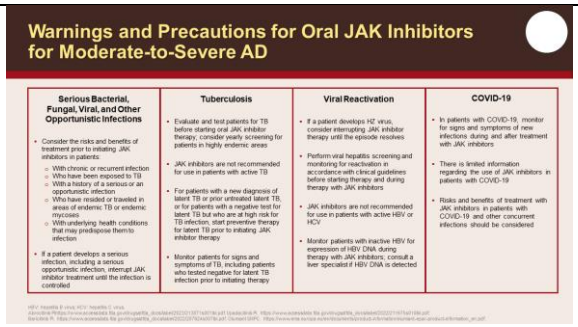
9		But infection colonization, it's also terminology that you do not always quite understand. It is important to understand that patients with atopic dermatitis and even nonlesional skin have a microbiome that differs from that of healthy skin. We see this dysbiosis. We see that the patient with atopic dermatitis have on the surface of the skin, *Staphylococcus aureus*. And if the patient having inflammation, and type 2 inflammation is the more prominent with a genetic predisposition, for example, filaggrin deficiency, this may lead to the increased colonization of *Staphylococcus aureus*. Furthermore, staphylococci can also produce some toxin, and this toxin may also allow that they easily can penetrate through the skin because they may cause the skin barrier disruption due to protease activities. And the skin barrier disruption again is leading to the further and more penetration of the *Staphylococcus aureus*. *Staphylococcus aureus* itself, it can also, as a superantigen, activate our immune cells like Th2 cells, and this will aggravate the disease; it may trigger an aggravation of the disease — it is leading to more and more inflammation. So, it is not only superficial infection or colonization that is the concern, but also the triggering and aggravation of the disease; therefore, infections are very crucial, especially in patients with atopic dermatitis.
10		Once we are looking to the *Staphylococcus aureus* colonization and if the patient have also problems of, where they have a clinically visible infection with *Staphylococcus aureus*, this may lead to the production of endogenous proteases, which can at one part also aggravate the disease to the point that it is increasing the substance P, increasing the IL-31, it's increasing the itch, and if itch occurs then we have a second problem. Because due to itch there are more scratches; due to more scratches, we have more lesions; and if we have in the area where we have erosions which are superficial, this is an ideal place where the bacteria can colonize and can penetrate and cause also infection in patients with atopic dermatitis. We do see that colonization, infection, and also

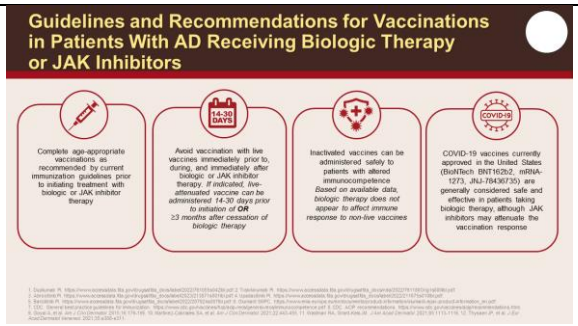
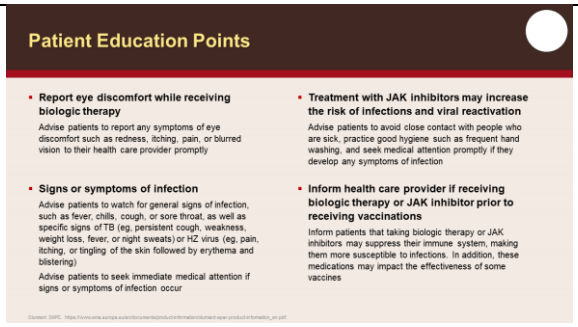
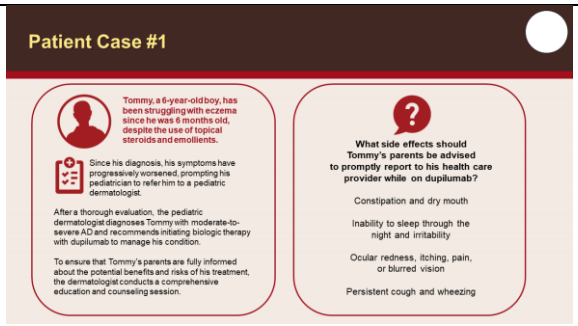
		dysbiosis with more pronounced *Staphylococcus aureus* is leading to the nonhistaminergic itch pathway, which means that it is causing not only the aggravation of the disease, not only triggering the disease, but also increase the itch in patients with atopic dermatitis.
11		Understanding this is also part of the pathophysiology of atopic dermatitis. We see at one side more acute inflammation, which is leading to the itch, which is at the beginning probably more superficial. But later on, we see the deep excoriations, which are with oozing and crusting with bacteria and especially staphylococci, can lead very fast to the colonization. We might see that around these scratches, around this excoriation, very fast we have also the occurrence of the inflammation bringing this together, that in patients with atopic dermatitis, we see that colonization but also infection and penetration of staphylococci is triggering at one side the disease, sometimes aggravating the disease, sometimes aggravating the itch, which is leading to the worsening of the clinical signs and symptoms of atopic dermatitis.
12		Finally, burden of disease, in general, of atopic dermatitis, especially because of itch and discomfort in patient with a skin infection, is the complaint of sleep loss. The patient cannot do their daily activities. The skin is not only itchy, not only burning, but it's also hurting. And also, due to the inflammation, is leading to more emotional stress. This is leading to significant health care burden, which includes also higher rates of hospitalization. At the other side, this also increases the costs of treating these patient. And in some cases, especially when we are talking about the eczema herpeticum, this can be also life-threatening. So sometimes we need also to act very fast. Especially in children where the risk can be also very, very high. At the other side, sometimes we use also antibiotics. Maybe also need, especially in a younger patient where we have a more severe infection, and this might cause also higher cost and may increase also antibiotic resistance.

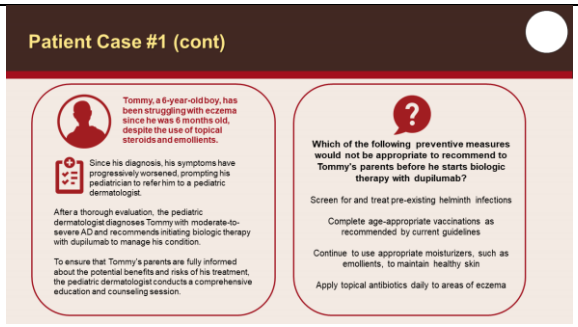
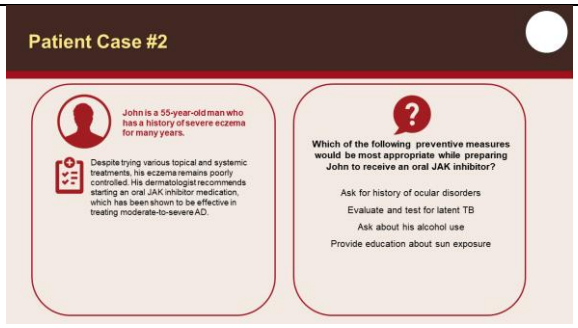
13		I think we are talking mainly about the cutaneous manifestation, the cutaneous infection, but sometimes we forget that patients with atopic dermatitis in general, they have a higher risk also for other infections. OK, chicken pox. We know this from the skin, but influenza and pneumonia, especially patients with comorbidities like asthma, is very frequent. Ear infection is also more frequent in patients with atopic dermatitis, as well as other infections. Even COVID-19 infection is more frequent in patients with atopic dermatitis, and this correlates very well also with the disease severity; in patients with more severe disease, we see even higher risk of COVID-19 infection.
14		And today, we have a different treatment option. According to the guidelines, we do have a stepwise approach where we start with a baseline treatment; mild, moderate, and severe diseases are also disease activity adapted, treated. While it is very important to understand the baseline treatment, which accompanies also the systemic and topical treatment because it helps, while it is important to understand baseline treatments that involves systemic and topical approaches, understanding the significance of emollients is equally important. Emollients are very important because they reduce skin dryness, a factor that facilitates the more effective colonization of bacteria, viruses, and other microorganisms, leading to skin infections.
15		When discussing systemic treatments, there are generally two main groups. The first group comprises biologics such as dupilumab and tralokinumab. Dupilumab inhibits IL-4 and IL-13, and tralokinumab only targets the IL-13 cytokine. Both drugs are highly specific and well-tolerated. The second group of drugs includes JAK inhibitors, specifically, JAK1 inhibitors such as abrocitinib, and upadacitinib. We also have baricitinib, which inhibits JAK1 and JAK2. These drugs interrupt the intracellular pathway that transmits signals to the nucleus and prevents the overproduction of proinflammatory cytokines. Basically, these treatment options, novel treatment options, have changed totally the understanding of

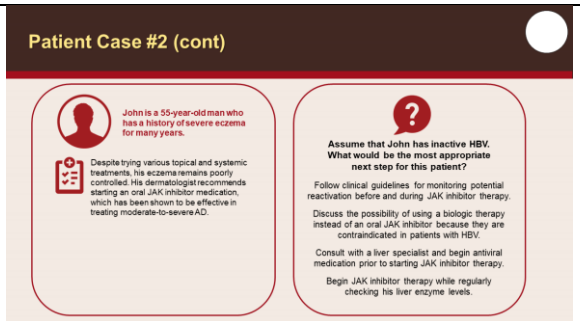
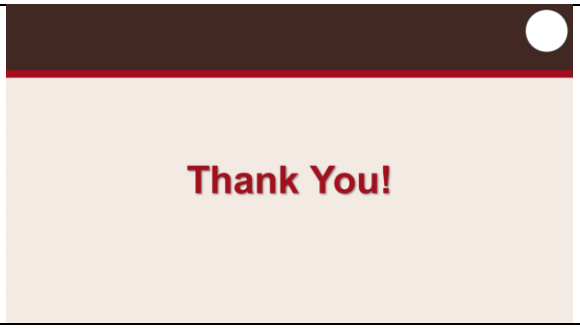
		the disease and have offered us better opportunities to treat our patients compared to the previous treatment with immunosuppressives like corticosteroids, cyclosporine, azathioprine, and also the others.
16		If you look to the biologics, if you look at the black box warnings, there are no black box warnings. Biologics have a very low risk, generally, of infection. For example, upper or upper respiratory tract infection, it's a very, very low rate with tralokinumab and also dupilumab. And also other infections, like herpes infection, also the others are not in the prescription information [in a black box warning]. If you go to the oral JAK inhibitors, we see they have a black box warning, especially the risk of serious bacterial, fungal, and viral and opportunistic infection; all of them — abrocitinib, upadacitinib, and baricitinib. And of course we have to take care, to take into account that the reactivation of TB can be also an issue, and also the activation of the viral infection may be also an issue. Therefore, it's very important before we start any treatment with oral JAK inhibitor to exclude and decrease the risk for any infection or reactivation of already existing diseases.
17		Looking from the data from clinical trials of dupilumab and tralokinumab, we do realize that comparing to placebo there are similar rates of infection, for example, oral herpes and also upper respiratory tract infection. But we see for sure, in the signal, patients who are treated with IL-4 and/or -13 inhibitor, dupilumab or tralokinumab, they do show a higher rate on the conjunctivitis. The question is, is this the conjunctivitis which is viral or bacterial? Today, we think that is not a viral and not really bacterial, either. However, we have to take into account and also differential diagnoses of bacterial or any other infection should be excluded.

18		From the data that we have seen in the clinical trials and also from the registries are showing to us and reassuring that treatment of our patient with biologics is offering to our patient even improvement of the risk from infection from herpes infection and it is not because these drugs are having antiviral effect. For example, dupilumab, it was shown, that we have reduction of herpes simplex compared to placebo in adolescents, but also in adults and also in the children. And I think this is merely not because of antiviral effect of this drug; it has to do more with improvement of the skin barrier, with improvement of the immunological status of this patient, with improvement of the dysregulation in immune system, more production of antimicrobial peptide, which is leading to reduction in serious and severe infections, which I think is very crucial in long-term management of diseases like atopic dermatitis.
19		And regarding the conjunctivitis, something is the dupilumab-induced ocular surface disease. I think this is something which is frequently occurring. It is mild and moderate; rarely it's very severe so we have to stop the treatment. And today we have opportunities. We know how to manage this disease (conjunctivitis), but it is crucial to differentiate between bacterial or viral causes, which are rare but should be considered. So, we need to advise our patients and tell them what might happen while they are treated with dupilumab. Sometimes this can be also observed with tralokinumab; numerically less, but it can be observed.
20		We know how to manage this disease (conjunctivitis), but it is crucial to differentiate between bacterial or viral causes, which are rare but should be considered. This was the opposite of prednisolone, of cyclosporine, of azathioprine, where the risk of COVID-19 infection was increased. So, therefore, for us is in understanding and the risk of the stomach infection we have learned from the COVID-19 that treatment with dupilumab is even having a positive effect, decreasing the rate of systemic infection, the viral systemic infection, which is also due to that that we are improving the immune status of this patient. We are changing also this imbalance in

		the cytokines, which is not the case with immunosuppressives.
21		The second issue that we usually look at in type 2 immune response, we do know that type 2 inflammation is there to protect us, to protect us against parasites. This is that what we have learned in the books; the parasites are that, why the type 2 inflammation is there, that production of IL-4 and -13 is there to protect the intestinal mucus and secretion and also peristaltic. This is also leading to the B cells to produce more anti-IgE to have the mast cell degranulation to fight the parasites and the same eosinophilic activation has to lead that our body should eliminate the helminths.
22		But this is also leading to something which is also important once we are treating with biologics, we have to exclude the helminth infection, they cannot co-occur. This is not happening in the north of Germany. This might happen in tropical and subtropical region. Also the reports are very scarce, but if the patient has any disease, for example cutaneous larva migrans, then treatment with biologic will not be probably the best treatment of choice.
23		And the second part of the treatment that we are usually also using in our patient are JAK inhibitors. We do see that infection rate is numerically higher in the JAK inhibitors, in abrocitinib and upadacitinib, but also in baricitinib we see a higher rate, especially on herpes zoster, more in the higher dosages and less in the lower dosages, and the risk generally of infection, viral but also bacterial, is slightly numerically increased in the patient who are receiving the JAK inhibitors.
24		What we see the major risk that we are facing is the risk of TB reactivation, which is rare in North America but can occur even in Europe and also in endemic countries. The viral reactivation, especially hepatitis B and C, can be of particular importance; therefore, vaccination against the hepatitis B and C is very, very crucial. Recently, during the COVID-19 pandemic, it was shown that JAK inhibitors may have negative effects on some infections of COVID-19. And generally, serious bacterial, fungal, viral, and other opportunistic

		infection have been shown to occur more frequently other patient who are treated with the JAK inhibitor, especially data from rheumatology are showing this kind of potential.
25		So finally, in the guidelines, which I think regarding how to treat a patient with atopic dermatitis with JAK inhibitors, I think it's important that we advise to do an appropriate, an age-appropriate vaccination, to avoid vaccination with live vaccine, for in this patient, inactivated vaccines can be used and the COVID-19 vaccines have shown that they are effective. But the question is, are they as effective as without the JAK? So it is necessary to interrupt the treatment with the JAK inhibitor before and slightly after the vaccination.
26		What I think is very important is that we educate the patient. That we tell them to report any eye discomfort. We should tell them that treatment with JAK inhibitor may increase the risk of infection, viral reactivation, but we'll do everything to avoid this. Signs and symptoms of infection should be also carefully observed by the patient and in case for example of eczema herpeticum, patients should know how to react and to inform us how can we help them much faster, much adequately, and much early in order to have the benefit of that?
27		Let me, at the end, show you a case. Tommy, a 6-year-old boy, has been struggling with eczema since he was 6 months old. Despite the use of topical steroids and emollients since his diagnosis, his symptoms have progressively worsened, prompting his pediatrician to refer him to pediatric dermatology. After a thorough evaluation, the dermatologist diagnosed Tommy with moderate-to-severe atopic dermatitis and recommends initiating biologic therapy with dupilumab to manage his condition. To ensure that Tommy's parents are fully informed about the potential benefits and risk of his treatment, the dermatologist conducts a comprehensive education and counseling session. So, what side effects should Tommy's parents be advised to be promptly reported to his healthcare provider while on dupilumab: constipation and dry mouth; inability to sleep through the night and

		irritability; ocular redness, itching, pain, or blurred vision; or persistent cough? And we see. So, I hope that you have the right answer. I think all of them, they are very important to report, but this is the one particular one which is occurring more frequently under the patient who are treated with dupilumab as a known adverse event which can be reported and should be reported during that period of time. This is ocular redness, itching, pain, or blurred vision.
28		Let me continue with Tommy again. Which of the following preventive measures would not be appropriate to recommend to Tommy's parents before he starts biologic therapy with dupilumab? Would **not** be appropriate. Screen for and treat preexisting helminth infection; complete age-appropriate vaccination as recommended by current guidelines; continue to use appropriate moisturizers, such as emollients, to maintain healthy skin; or apply topical antibiotics daily to areas of eczema? Very curious to hear. Of course, not to use topical antibiotics daily. This is totally counterproductive, something which we should avoid in our daily practice.
29		Another case. John, a 55-year-old man who has had a history of severe eczema for many years. Despite trying various topical and systemic treatments, his eczema remains poorly controlled. His dermatologist recommends starting an oral JAK inhibitor medication, which has been shown to be effective in treating moderate-to-severe atopic dermatitis. Which of the following preventive measures would be most appropriate whilst preparing John to receive an oral JAK inhibitor: ask for history of ocular disorders; evaluate the test for latent TB; ask about his alcohol use; or provide education about sun exposure? Everything is important, but I think that what is very important: evaluate and test for latent TB.

30		
31		I think this is very important for all of us. We have to take care about our patient. We have to be very cautious how we are managing this. However, in the daily life, some of the dysbiosis might be also productive. Contact with microorganism very early we should not avoid, infection is not a contamination. Our microbiome should be interacted and sometimes we are learning that once that was in the past avoiding the microorganism, it was not the solution. The solution was always to try to find out how can we have a steady-state disease that the skin is always in the contact with the microorganism, that we have this heterogeneity of the microbiome, which will allow us not to have the colonization with *Staphylococcus*. So, I think this is something that we are learning again and again: Hygiene hypothesis is not optimal, but that what we have to care about in our patient is infection, either they're cutaneous or systemic.
32		With this, I would like to thank you very much for your attention.