Prevention research

I'm excited to introduce Dr Helen Brough, Dr. Brough is a consultant and pediatric allergist and head of service at Evelina London Children's Hospital. Her research interests include early intervention and prevention of allergic conditions of childhood. Dr. Brough is leading the multi center European Pronut Study and was co-author of the LEAP or Learning Early about Peanut Study, which was a landmark study. She's really going to move us from how do we detect this to what can we really do about it? And what are those best strategies for prevention once we know a child is high risk. So, thank you very much Dr. Brough for joining us today.

Thank you so much for the kind introduction. I'm going to be talking today about addressing skin barrier defects early to treat and prevent atopic dermatitis.

So, to start with I'm going to talk about some of the things that break down the skin barrier, particularly the detergents, through which environmental pollutants and infections then lead to an impaired skin barrier function. So these are all contributing factors in addition to genetic predisposition and it is a complex interplay.

And then that can lead in itself to food sensitization and allergy which can then lead to skin inflammation. My daughter also has eczema and I do see that her skin is fine but she's scratching it and then that's when I see the changes of the skin.

Skin microbiome

So we know that disruption of the skin and of the gut is a predisposing factor towards the development of atopic dermatitis. We know that the skin microbiome in children that have eczema is different from children that have healthy skin. You have an abnormal skin barrier and abnormal microbiome even at rest, which then becomes more abnormal, more Staph aureus less commensals, when there's a skin flare,

Gut microbiome

Also, I think there's been a reduction in diversity, both in our gut microbiome and in our diet. And this means that what we have is more pathogenic bacteria strains and less of the friendly strains in the gut. So the Staph aureus can be increased, Clostridium difficile can be also implicated. Whereas the good bacteria like Lactobacillus and Bifidobacterium, if they're reduced, can then increase the risk of development of atopic dermatitis. And we know this from fecal samples before the onset of eczema.

Probiotics

There's a lot of interest in probiotics for eczema prevention, and from a therapeutic mechanistic understanding, there are many different ways in which you could potentially see probiotics preventing eczema by helping to mature the dendritic cells, increasing T regulatory cells, reducing the inflammatory responses which then leads to downstream signalling of allergic pathways. And then by directly improving barrier function. However, the studies that have looked at actually supplementing probiotics have not been as successful as we would have hoped.

And the only guidelines that even give a weak recommendation for probiotics are the World Allergy Organization, and they recommend probiotics for pregnant women in their final trimester and breastfeeding women and infants. A study that looked at probiotics for the prevention of asthma published in 2015 for pregnant uh, breastfeeding and infants. And it was shown to favor probiotics. But some of the issues is that they looked at lots of different bacterial strains and the designs of the

studies were all very different. Since then, there's been another systematic review and meta-analysis. And this was published in 2019, and they did show that probiotic treatment was associated with a reduced risk of atopic dermatitis, but that you needed to do it both in the prenatal and postnatal period. And there's a lot of interest in this because the fetus is exposed to the amniotic fluid which has microbes in it from the mother. And there's a belief that there's some imprinting or some programming that occurs in the fetal gut that allows it then to be more resilient against some of the more TH2 um, influences. Particularly, for example, if the child has a C section and therefore is not exposed to the microbiome from the birth canal. This may be why just doing them postnatally doesn't work. But only giving them prenatally also doesn't work. So you need to have that continued supply of the protected microbiome before and after birth.

Skin barrier therapy

Skin barrier therapies. Again, it would be wonderful if we could just find a nice cheap cream that we could put on the child's skin from birth, and that would solve all our problems, protect the skin barrier against all of those nasty things in the environment, those peanut allergens that then drive peanut allergy.

However, unfortunately, looking at some pretty large studies, there was no significant impact of using emollient therapy in children from birth to prevent the development of eczema. This was published in 2021. And then shortly after that, there was another meta-analysis, which did a little bit more stratifying and looking in detail.

And they found that if they looked at just the high risk population with preventative emollient therapy, that there was some reduction in atopic dermatitis. And they said also, when they looked at different studies, looking at whether they assess the eczema whilst they were still applying the creams or after a gap in applying the creams, that the children who were still having the creams applied had a reduction in atopic dermatitis, which suggests that perhaps this treatment could prevent the development of eczema by delaying it. So it might come later once you stop the creams. But that would provide enough time, at least, to get some of the food allergens into the diet through oral tolerance induction.

The STOP AD study, which has happened since then, goes very much against what the previous meta-analysis showed. So this was done in Ireland, with Jonathan Hourihan's group. And there they have a very sort of different way of managing mothers after birth. They are all routinely kept in hospital for three days. And because of that, they're able to do a lot more promoting breastfeeding, etc. But in this particular study, what they were able to do was recruit 321 high risk infants, whose parents have a history of atopy. And they were given a ceramide containing moisturizer for eight weeks from birth. And so these children have the emollients applied from very, very early on in life. Around three days of life is when they first started, which is much earlier than all of the other studies. And they showed that in the children that had the moisturizers applied just 8 weeks from birth, there was approximately 50 percent reduction in point prevalence of eczema at 12 months and about a third reduction in cumulative incidence of eczema at 12 months. Now, there were no differences in skin infections during the 8 week intervention period and this is in difference to the other study called the BEEP study where there was an increase in skin infections. And this study happened after the BEEP study, so lessons had already been learnt about ensuring that parents wash their hands before applying creams.

Ceramides and food sensitization - PEBBLES

And then going back to the trilipids story, which is the ceramide story, there's quite a lot of data which shows that trilipid creams can improve the skin barrier. And this is a pilot study, in Australia, showing that in children that had trilipid creams applied from around the time of birth there was a not significant improvement in visible eczema at 12 months, but what they found, which was really interesting was that was 0 percent sensitization to milk, egg, or peanut at 12 months.

Summary

So, to summarize, the petrolatum based creams may delay eczema, may prevent eczema in high risk children, and there may be an impact of time of cessation of treatment and assessment of AD on this.

And then there potentially is an increase in skin infections if the right advice is not provided about washing hands before applying creams. Trilipid creams showed a 50% reduction in point prevalence of atopic dermatitis.

And the PEBBLES study in Australia also showed positive trends for atopic dermatitis prevention. And there's a much larger study be carried out in Australia and we are awaiting the results of this.

SEAL study

This brings me to the SEAL study, which is a NIAID funded multi PI study in Stanford, National Jewish Chicago, our site, and Harvard. We're looking at whether children between the ages of 0 to 12 weeks of age can have food allergy prevented and, of course, eczema treated and prevented from having flare ups with proactive skin care.

We're using two different types of emollients, AVEENO versus trilipid, and we're using proactive steroids, which means using topical steroids twice weekly after you've maintained the flare of the eczema for 16 weeks to see if this can prevent food allergy. And this is ongoing, we've recruited approximately 200 participants.

Future directions

Future directions. I've talked about moisturizers. I've talked about proactive therapy with topical corticosteroids. There are many other therapies, filaggrin replacement, filaggrin enhancement, JAK inhibitors, AHR agonists. So there's a lot going on and then there's a lot working in the skin and the gut microbiome as well.

Take home message

So my take home messages: probiotics used during pregnancy and in the postnatal period may reduce the risk of developing atopic dermatitis. The issues with different study designs and different species all being lumped together is making it difficult to interpret and so more data is required.

Emollient use in infancy may prevent eczema in children who are atopic, but not in children who have non atopic parents. I always have a real plug here to make sure that the families are not inadvertently putting bacteria on the skin by not washing their hands before applying creams or by putting their hands inside a pot of emollients.

So ointments, for example, usually come in these big pots, and then people put their hands inside, apply it on the child's skin again, put their hand inside again, and there's good data to show that they're contaminated with bacteria. We know that bacteria then make the skin more inflamed and increase the risk of developing food allergy.

The STOP AD trials show that early ceramide emollient use in infancy may prevent asthma and food sensitization, but actually getting that into clinical practice in the way that they did would be very hard because you'd need to have a setup like they did. They actually stopped the study after they saw the beta study findings, because they thought it was not worth continuing to follow up the families to see if they were preventing food allergy, but then since they have these dramatically positive findings, they now have funding to assess these children at 4 or 5 years of age for food allergy. So we are awaiting this data.

Thank you. Dr. Brough, I think one of the things that I take away from your summary is that: These strategies for how to prevent eczema and food allergy need to be very nuanced in how we do them, the method that you choose, the timing when in childhood is important the exact type of intervention that's used what probiotic, what emollient… these things all matter. And I appreciated how the latest research sheds light on those details to help us pinpoint what's really going to work.

We do have some questions and I think one that I wanted to ask was: given what we now know, what are the critical unanswered questions that need to be resolved in order for prevention strategies to become adopted and for us to really be able to ward off eczema in early childhood?

I think, to be honest, getting the basics right is where we start. So not inadvertently causing more harm by putting bacteria on the skin by advising people to wash their hands before applying creams. By not giving them pots, which they put their hand into, really basic things like that. There's so much misinformation about eczema. When the parents see that their child first has eczema, the child probably only has eczema, which is mild to start with, and they're given all the wrong advice. And then eczema gets worse and worse and worse and worse. And then they come and see a specialist, but by that time, the child has already had eczema for about two or three months. And some of the damage is already done. I think free online educational resources are incredibly important. We have to make this accessible to all people. Eczemacareonline.org.uk is a wonderful online site, designed free from industry, created by parents and adults that have eczema. It just gets all the messages across properly, and people are really scared of using topical steroids, and so they don't use them, and then they get, you know, really terrible eczema, then their child has to have oral antibiotics, which then damages the gut microbiome further.

So I think before we start going into JAK inhibitors and all this kind of stuff, we just need to get the basics right. So that when a family gets in with a mild eczema that they get access to the right information, they can manage their child's skin really well, really quickly. Not put creams on their skin that have peanut oil or sesame oil that could potentially lead to food allergy.

Just, just get the basics right. I think that's really where I'm at because I see so many families with... Such, I feel so bad for them. Their babies are so badly affected with eczema and if only they'd been given the right advice, you know, several months ago the whole thing would have changed.

Wonderful, thanks for that answer. And we'd love to share that resource, so we are now at time. Thank you so much Dr Brough and have a wonderful rest of your day.

Thank you for your attention.