So good day everyone, my presentation for today is Severe Asthma: Can Phenotyping Help with Understanding and Treatment? So severe asthma actually should be considered as difficult asthma when a patient certainly presents to you initially; and what we mean by difficult asthma is asthma that requires high intensity treatment when you see those patients and despite being on high intensity treatment they actually achieve good control only if they are on that high intensity treatment or they never achieve control, they have poor control despite that high intensity treatment. So when you see those patients coming into your office with difficult asthma, you then need to do some initial subgrouping of those particular patients. And certainly when you think about these patients with difficult asthma, you need to first of all determine whether they actually have asthma or not, because a good percentage of individuals that come to you with difficult asthma may actually not have asthma, they may have vocal cord dysfunction, they may be obese, they may even have elements of malingering but not have true asthma.

If they do have asthma, you then need to determine whether they are actually potentially treatment responsive asthmatics. These are people who perhaps working with them, improving their compliance, maybe removing allergens from the home, like they are allergic to cats, stopping smoking, etc., all of those things may have a very large impact on improving their disease. But then you are left with probably the remainder of the, the group of patients who have either persistent comorbidities that are actually very difficult to treat like persistent sinusitis, maybe some psychosocial issues, even obesity can be pretty difficult to treat. Or they are truly treatment resistant asthmatics, so despite whatever you do for these individuals there is really nothing that you can do to
improve these patients, or at least very little, and these are patients who are generally termed refractory asthmatics. So I think it’s important when you see a patient with difficult asthma to initially put them into this sort of bigger picture of subtype.

And again, I think this is very important because believe it or not in our practice when I get referred patients with difficult asthma, in our initial 150 or so patients with difficult asthma that were referred to me, about a third ended up not having asthma at all. And I think you can see from this pie chart that about a third of those individuals gave no evidence for asthma, even with Methacholine challenges, good pulmonary function tests, etc., there was no evidence that those individuals really did have asthma. And of course, treating patients who don’t have asthma with asthma medications is never going to improve their symptoms and their outcomes.

So when do you actually have to think about masqueraders for patients who come to you with difficult asthma. And I think again, I don’t, I want to emphasize how important this initial subtyping is. You want to think about masqueraders when a patient comes to you who has normal spirometry, so normal lung function but their symptoms are out of proportion to their FEV1 percent predicted. Or you have a patient who has actually abnormal spirometry but maybe they have an atypical pattern to their symptoms, maybe they have a poor response to medications. Those are the times to really think about maybe this isn’t actually asthma.
So when we think about normal spirometry with positive symptoms I think there are three things that should come to mind. Certainly you can have brittle or episodic asthma. In adults that’s actually very, very rare. So patients who actually have no symptoms on a day to day basis, normal lung function and then all of a sudden have a very severe exacerbation, those patients are very rare. But you should certainly keep them in mind. Probably the most important thing to consider is whether a patient has vocal cord dysfunction or upper airway obstruction and I’m going to go into that in a little bit more detail; and then certainly just regular old anxiety attacks can potentially be misdiagnosed as asthma as well.

So vocal cord dysfunction often presents with episodic but a dry cough, episodic chest tightness which often occurs right below the neck and patients will often actually give you a sign that they will almost reach for their neck and say when I get chest tightness it’s right here, right under my neck. They will also often tell you that they have a difficult time getting their breath in, much more than getting their air out. And of course asthma is a disease of expiratory air flow limitation, vocal cord dysfunction is actually a problem with inspiration, so there’s closure of the vocal cords during inspiration. In all of these cases you can have an association with gastroesophageal reflux disease, that is a very common comorbidity, or postnasal drip. And sometimes when you have postnasal drip you can actually have patients present with a productive cough, so it doesn’t always have to be a dry cough. But many times you’ll see those comorbidities coexisting.
Vocal cord dysfunction was initially described in women often with a history of sexual abuse, and I think it’s still associated with an anxiety, anxious personality. Interestingly, it’s very common in young people, in elite and highly competitive athletes and it’s often mistaken for exercise induced bronchospasm, but certainly is quite easy to distinguish from exercise induced bronchospasm because these are patients who often times either at the very beginning of a race, or right before they get to the finish line will have a very sudden onset of inability to breath, inability to get their air in, and when you do analysis when you do studies you actually find out that this is a vocal cord problem as opposed to exercise induced bronchospasm.

However it’s now appreciated to also be present in both sexes, it’s most commonly seen in association with postnasal drip and gastroesophageal reflux disease, which I’ve often – which I’ve already alluded to. And treatment often improves the vocal dysfunction, so just focusing on improving their postnasal drip or their reflux can actually improve their symptoms. And I think some of this association of gastroesophageal reflux disease and heartburn actually may explain some of the previous associations that we’ve had with gastroesophageal reflux and asthma because vocal cord dysfunction is so commonly mistaken for asthma.

Now how do you diagnose vocal cord dysfunction? Again, one of the most common masqueraders of difficult asthma, it’s diagnosed by demonstrating paradoxical inspiratory closure of the vocal cords. And this actually can occur spontaneously or you can induce it, you can induce it with things like perfume, by Methacholine challenges and by exercise. But you want to have an appropriate
history, you want to have flow volume, spirometry flow volume loops which are supportive of that, and then definitely you want to be able to look down at the vocal cords and actually see that there is closure of the vocal cords during inspiration.

These are some examples of spirometry that you can see. Normally one would have almost mirror images of the curves below, below and above the X axis, but in patients with vocal cord dysfunction there is a cutoff of the inspiratory flow volume loop such that within very early on after beginning inspiration there is a decrease in the flow that occurs, and patients don’t maintain a good flow but then they exhale completely normally, and that’s what we see in association with vocal cord dysfunction, which discriminates it from asthma.

And when you look down at the vocal cords through a laryngoscope what one sees is closure of the vocal cords during inspiration. During inspiration the vocal cords should be almost completely open, you can have partial closure, you can have full closure or you could have even just some little twitches, but all of that I think is suggestive. And certainly you can have irritation of the arytenoids in the epiglottis if there is concurrent gastroesophageal reflux disease, so it’s important to look for that as well. And certainly in some cases patients can have asthma as well, so it’s, it’s important to remember that they may have both vocal cord dysfunction and asthma, although generally speaking it’s pretty easy to distinguish the two.
Let me move now to someone who presents with difficult asthma but who has abnormal spirometry. And certainly I like to divide the abnormal spirometry into those that have an obstructive pattern, a restrictive pattern or a mixed pattern. And in an obstructive pattern I’m talking a low FEV1 and a low FEV1 to FVC ratio, probably the biggest confounder or masquerader is COPD. And I have to say from my experience often times there is a hesitation to diagnose asthma in a young person, excuse me a hesitation to diagnose COPD in a young person who is a smoker. So you can have someone who has smoked for 20 pack years, they are 40 years old, but no one wants to call that person COPD at the age of 40. They would rather call them asthma. But when you actually do the extensive evaluation, to look do they have a diffusing capacity problem, do they have emphysema on CT scans you find that they actually have COPD as opposed to asthma.

Allergic bronchopulmonary aspergillosis should also be considered in patients who have a very strong allergic history. Often times these patients will get their disease in adulthood and will have high levels, very high levels of IgE and very high levels of eosinophils in their blood which are helpful to distinguish from just garden variety asthma, and then constrictive bronchiolitis often with either an autoimmune history or some exposure history. A restrictive pattern while most commonly we think of restrictive patterns in relationship to interstitial lung disease, when you are talking about masqueraders for asthma I think the most common masquerader is just obesity. So patients who are very obese can’t actually get as big a breath in as individual who aren’t that obese and it leads to the development of restrictive pattern. Sometimes these individuals actually are very short of breath and because they are very short of breath, because they are deconditioned and obese and have a low
FEV1 but not a low FEV1 to FVC ratio, they are actually confused and called asthma and treated for such.

And then you can have people who have a mixed pattern. So they have a low FEV1 and a low FVC but their ratio is still low, so they have elements of both obstruction and restriction and certainly from that perspective I think the, the two most common masqueraders are hypersensitivity pneumonitis which certainly can mimic asthma in many cases, sarcoidosis as well as very rarely a Churg-Strauss syndrome.

Well let me move on now to actually the group of patients who have asthma. So we’ve now ruled out patients who don’t have asthma presenting with difficult asthma, now it’s important to actually try to begin to understand these difficult asthmatics better. And I like to describe the 3 As as I call them, asthma, arthritis and anemia. Well really how are these all alike? Well basically they are all nonspecific, general characteristics of disease. They describe swelling, swelling in the joints, low red blood numbers or in the case of asthma reversible airway obstruction. And those terms shed almost no light on what caused these characteristics to develop.

And if we focus specifically on arthritis, no self-respecting rheumatologist would ever ultimately diagnose a patient with arthritis as the natural history, the genetics, the inflammatory processes and the response to therapy differ by which arthritis the patient has, i.e. understanding the – i.e. the
understanding and the treatment of rheumatoid arthritis would be vastly different from the treatment of osteoarthritis. So it’s very important to put those in context.

Now we are not quite as far along in the asthma world as we are perhaps in the arthritis world, and so in asthma we are still referring to asthma phenotypes. Well what is a phenotype? So a phenotype is the characteristics with an emphasis on pleural, characteristics, of an organism which result from the interaction of the genes with the environment. And in severe asthma as our knowledge increases it seems that some of the biggest differentiating features of asthma phenotypes include when did you get your asthma, what is the type or the extent of the inflammation associated with asthma, and how severe is your airway obstruction?

So I like to think of asthma as really an umbrella term. And asthma encompasses patients who present to you with symptoms, with exacerbations, with changes in their lung function, changes in FEV1, very nonspecific sort of factors. And I think we are now getting to the point where we can actually begin to assess whether there is inflammatory components that are, that are contributing as well. And I’m going to show you some data to support a group of asthmatics who have Th2 inflammation, an adaptive immune response and then some individuals who have very little evidence for this Th2 inflammation. But in any case, you’ve got probably 3 or 4 or 5 or maybe 10 different phenotypes that can actually arise and all still fall under this umbrella term of asthma.
Now probably the easiest group to identify is a group that actually is pretty easy to identify clinically, and these are patients who present to you with difficult asthma and they tell you I’ve had my asthma my whole life. I got it when I was a child somewhere between the ages of 2 and 5, maybe it was severe from the start, maybe it wasn’t, maybe it progressed, but it developed early on in life. And I think many studies are now suggesting that early onset asthma is very distinctly different from later onset asthma.

This is a study that we published in 2004 where we looked at about 100 asthmatics, and we divided them into those who got their disease before the age of 12 and those that got their disease at the age of 12 or later, and we called them early and late onset. And we looked at their allergy, their predisposition to allergy and HOP. So we did skin testing and we looked at skin test reactions to various allergens, and nearly 100% of early onset asthmatics actually were atopic by skin testing, so they had at least one allergy skin test that was reactive. Now late onset was also reactive, 75% of those or so had positive skin tests, but very significantly different from early onset disease. But then I think more importantly when we actually asked do you have allergic symptoms, allergic asthmatic symptoms most or all of the time when you are around dust, when you are around furred animals, seasonal changes with pollen and nearly twice as many of the early onset individuals said yeah, I recognize I have those symptoms as compared to late onset disease.

If we looked at a history of eczema, atopic dermatitis 40% of early onset individuals said yes, I have that history; late onset individuals, only 4%. IgE levels tended to be higher in early onset, again
consistent with an allergic process. And the family history of asthma was much stronger in early onset disease as compared to late onset disease. I think supportive of a genetic component to individuals with early onset asthma. Well that was sort of my clinical impressions of patients that I see in the clinic. But there are certainly statistical ways to try to analyze these asthma phenotypes as well. And at least from a couple of statistical approaches to understanding phenotypes there has been a very nice confirmation that age of onset of disease is an important differentiator of asthma phenotypes.

And this one that was published last year, it was done on the Severe Asthma Research Program which is an NIH sponsored network of severe asthma patients. It was a cluster analysis performed at Wake Forest and it included 304 severe asthma subjects who really were severe by, by every rigid criteria including high doses of inhaled corticosteroids and even oral corticosteroids. And they actually analyzed 628 different clinical variables and they compressed them into 34 weighted variables for a final analysis. And using that statistical approach they were able to separate 5 different clusters. And the 3 strongest predictors of which cluster you fell into was your lung function, did you have airway obstruction and how severe was it, and your age at onset. So it wasn’t HOP or allergy, it was just that simple question, when did you get your asthma? And interesting there is now even genetic studies that also support this importance of age at onset. The genetic studies track much better with when you got your disease as compared to whether you have HOP or allergies.
SEVERE ASTHMA: CAN PHENOTYPING HELP WITH UNDERSTANDING AND TREATMENT? SALLY WENZEL, MD

So these are sort of the three clusters that fall into the classic allergic atopic early onset disease as identified in the SARP statistical analysis. And they go from mild to moderate to severe allergic disease. And with that increase in severity you have an increase in duration of disease, patients having their asthma 15 years in the mild group, 30 years in the more severe group, again they are all atopic and allergic, they all got their disease early in life and I think this really suggests that there is some genetics that are involved in atopy and allergy that influence the development of this phenotype early on, that there are probably some environmental factors that help push you over the years from a mild group to a moderate to a severe group, but there’s also probably some additional genetic factors that are you know poorly understood at this point but which may help to move you from a mild to a moderate to a severe asthmatic.

Interestingly in the severe allergic asthmatics a good percentage of those severe allergic asthmatics had had pneumonia at some point in their life, and so it’s very possible that infection played a role in moving you from a moderate to a severe asthmatic. But once you were in that very severe allergic early onset disease group you were identified by having a highly reversible disease, you had a lot of air trapping and interestingly you had the greatest number of allergic skin test reactions. So you were highly allergic. And I think all of those things combined to allow you to become this, this severe asthmatic.

Well identifying this subgroup with allergic early onset asthma I think supports the use of targeted therapies, and of course we are getting better in, in our understanding of the pathobiology that goes
along with allergic asthma, and there’s been at least one successful approach I think to targeting allergic asthma and that’s with anti-IgE or Omalizumab. These are just data from the early pivotal trials where basically patients with moderate to severe asthma, allergic asthma as identified by skin test reactivity and IgE levels were treated with Omalizumab compared to placebo and the group that got placebo had a significantly greater number of hospitalizations due to serious asthma exacerbations as compared to the group that got Omalizumab where the exacerbations were quite markedly reduced. So again targeting an allergic component in an allergic phenotype seemed to lead to efficacy.

But I think our understanding is progressing so that we understand that allergic inflammation is actually a lot more than just IgE. And certainly with IgE we’ve focused on sort of the mass cell degranulation affects and blocking the ability of mass cells to degranulate with an IgE mediated process, but there’s a lot that promotes this IgE armed mass cell as it were, and some of that involves dendritic cells, some of that involves adaptive immunity with a Th2 sort of response. The Th2 cells are making IL-4, IL-13, and that certainly promotes then the production of IgE which then leads to this allergic response that is treated by the Omalizumab. But there’s all these things that are going on to the left of this IgE mediated process as well that could be contributing and likely are contributing to the inflammatory process.

Well what’s our – what’s the evidence that there actually is a Th2 adaptive immune process with – that is associated with this allergic atopic phenotype? I think there was a very important molecular
phenotyping study that was published in 2009 from a group at UCSF which they actually did some initial analysis of cultured epithelial cells. And they stimulated those cultured epithelial cells with IL-13 and they tracked what were the most important factors that were produced by those epithelial cells and they came up with three factors, Periastin, CLCA1 and SerpinB2 as markers for what Th2 stimulated epithelial cells made. And then they went back and looked in mild allergic, mild asthmatics for the expression of these particular factors in freshly obtained epithelial cells from the airways using a bronchoscopy approach from the airways of these mild asthmatics. And what they found I think was very striking and somewhat surprising. So these mild non-steroid treated asthmatics only about 50% of these mild asthmatics actually expressed these Th2 related factors. And those are the patients with the As underlining the portion there who have orange in the blocks above them, that is the Th2 high group. But about a third had actually no impact, no evidence of expression of this Periastin and these other mediators, and really were mixed in with the Hs, which are the healthy controls, so there was no difference in this Th2 phenotype compared to these healthy controls.

But if you fell into this group that had the high expression of these factors you were in fact much more likely to be atopic or allergic, to have greater bronchial hyperresponsiveness and to have more eosinophils in your airway. And they went back and actually looked for the expression of Th2 cytokines and those individuals had more Th2 cytokines in their airways as well. So it seemed to very strongly support that there was in fact a Th2 high subgroup of mild asthma.
And when they looked further this Th2 high group of individuals had more airway remodeling, so if you looked at sub-epithelial basement membrane thickening under the epithelium, significantly higher in those individuals that were Th2 high as compared to Th2 low; but I think the most important thing that they showed in this study was that if you were in the Th2 high subgroup and you were then treated with inhaled corticosteroids, in this case Fluticasone, there was a significant improvement in lung function in the Th2 high group over the 8 weeks of the study, whereas there was no effect of inhaled corticosteroids if you do not have evidence of this Th2 high phenotype. And I think this is very important to remember as we move forward and we are considering treating our patients with inhaled corticosteroids if a patient falls into a Th2 low phenotype they may not respond to corticosteroids at all. And so I think there is great clinical applicability of those findings.

Now in addition to having this increase in eosinophils, this increase in this subepithelial basement membrane and the increase in response to corticosteroids in this Th2 high subgroup, there are also data to suggest that this Th2 high subgroup is associated with an increase in mass cells. And I’ve already sort of associated mass cells with IgE and a Th2 process so I think this begins to connect them a little bit. And in looking in the biopsies there were higher numbers of mass cells in those individuals that had Th2 high cytokine, Th2 high factor expression in their epithelium. And I think this has implications again for treatment beyond anti-IgE because there is a great deal of interest right now in developing antagonists of a pathway that’s related to mass cells, the Prostaglandin D2 pathway and a receptor called CRTH2 and at least in studies that we’ve been doing and that were published in the American Journal of Respiratory and Critical Care Medicine in 2011 if we look at
patients with severe asthma who are symptomatic, have a high degree of nocturnal symptoms going to the hospital at least once in the last 12 months, or have a low FEV1, those individuals have a very high level of this mass cell specific mediator called Prostaglandin D2. And again I think I want to share this because there is great interest in developing antagonists for this particular pathway and I think at least from a phenotypic approach this pathway may very well have clinical relevance and be effective – may lead to effective treatment.

Now phenotyping should also improve our ability to genotype. So one of the things that I mentioned early on was that early onset asthma seemed to track much more strongly with genetics, family history than late onset disease did. And I think certainly when one things of early onset asthma I try to build the story for a Th2 inflammatory process. Th2 cytokines include IL-4 and IL-13 but these are other factors including the receptors, the IL-4 receptor alpha and all of these have had genetic polymorphisms described in them that are associated with asthma and HOP. And at least from a study that we published in 2007 certainly is – these genetic polymorphisms also seem to be associated with a severe exacerbating type of asthma, low lung function and interestingly an African-American, or an African racial background. So some genetic changes in this Th2 pathway seem to track with more severe types of asthma.

But when we look at our early onset atopic clusters as I showed you earlier with increasing severity of early onset disease, interestingly if we look at some of these genetic factors and we focus specifically on a genetic factor in the receptor for IL-4 and IL-13 what we find is that this risk allele
actually tracks very nicely with increasing severity of disease that those individuals that are the most severe allergic asthmatics, nearly 50% of them have expressed this risk allele whereas only about 30% of the mild allergic asthmatics actually express this allele, so almost a dose response in relationship to severity.

Now it’s important to say that the proof that the Th2 pathway is important in, in allergic early onset asthma actually depends on blocking that pathway. And although we’ve talked about blocking this pathway for years, and there were some early studies that actually tried to block the IL-4 itself, there really wasn’t data to support that. And I think in the last few years that is an increasing signal that the Th2 pathway is in fact important in at least mild allergic asthma. So there is a molecule called Pitrakinra which is an IL-4 receptor, excuse me which is an IL-4 mutant molecule, it binds to the IL-4 receptor and when it binds to the IL-4 receptor it prevents the IL-4 receptor from dimerizing with its other component. These are the common gamma chain or the IL-13 R alpha 1. And by preventing dimerization it prevents any signaling from occurring in that pathway. So it really serves as an IL-4 receptor antagonist.

And in studies in an allergen challenge induced exacerbation, so mild allergic asthmatics not treated with any medications, exposing them to an allergen that they are allergic to for a period of time and then looking at their change in lung function what normally happens is that if you expose one of those asthmatics within about 15 minutes or so you’ll have an immediate fall in their pulmonary function. They then return to their baseline within about an hour and they stay there for a couple of
hours, and then somewhere before 4 to 6 hours they have a second fall in their lung function and that’s called their late asthmatic response.

So in this study they actually treated patients with placebo or with this IL-4 receptor blocker for about 4 weeks, and then they repeated that allergen challenge. And you can see that with the placebo group there was absolutely no change, exactly the same. But when they were treated with Pitrakinra, this IL-4 receptor blocker, there was about a 30% reduction in that early response to allergen and about a 50% reduction in that late response to allergen. And again I think that’s very confirmatory that at least in an allergen challenge asthmatic response that the IL-4, IL-13 pathway is certainly playing a significant role.

What’s also interesting is that in addition to protecting against a change in lung function, protecting against this fallen FEV1, there also seemed to be an effect on allergic inflammation. So this is measuring exhaled nitric oxide, exhaled nitric oxide is an inflammatory factor that’s measured in breath and certainly when patients were treated with this IL-4 receptor blocker you can see that there was about a 40% reduction in this exhaled nitric oxide, and that tended to decrease even further after an allergen challenge. And interestingly it was significantly different from placebo where there was absolutely no change. If you look at these genetic factors there is also some data to suggest that having some of these genetic factors may also predispose you to having a better response to this IL-4 receptor blockers. So there may be a pharmacogenetic impact as well in these response to these particular targeted agents.
Well I’ve been talking primarily about early onset allergic asthma and I think we understand a lot more about early onset allergic asthma than we do some of these later onset phenotypes. But it’s important to mention them because there is a very good percentage of patients with difficult asthma that have these later onset phenotypes. And so asthma that occurs later on in life is defined as occurring somewhere around the age of 12 or later, it’s much more heterogenous than early onset disease, there is likely contributions from aspirin sensitivity, infection, hormones, obesity, occupational exposures, diesel exhaust being increasingly recognized, tobacco smoke and certainly allergies can’t be completely excluded. But because of this heterogeneity I think treatment by phenotype is almost certainly going to be important.

Now contrary to popular belief, eosinophils in the airway are actually more common in adult onset disease as compared to early onset disease. So although we’ve often thought about allergic asthma as an eosinophilic disease, persistent eosinophilia is more common in late onset disease. And whether you look at this by a clinical approach or whether you look at this with an unbiased statistical approach, everyone can identify late onset disease associated with eosinophilia. These are again data from our clinical approach where we actually did biopsies of patients with early onset disease compared to late onset disease, and you can see there is a statistically significant higher number of eosinophils in the airways in patients with late onset disease as compared to early onset disease.

And then in a statistical analysis that was done in the United Kingdom, they were able to identify the same allergic, early onset allergic asthmatics in the, in the ellipse in the middle, but they identified in
the lower right hand corner a group that had eosinophilic inflammation, inflammation predominant, late onset disease, greater proportion of males and a high degree of eosinophilic inflammation. So again, statistically supporting what we observed clinically.

So this hypereosinophilic adult onset asthma, these are adult onset patients, highly eosinophilic asthma despite high doses of inhaled and even sometimes oral steroids, they are often severe from the start, they often only respond to systemic corticosteroids, i.e. Prednisone and Medrol. Sometimes they respond to a 5 Lipoxidase Inhibitor, i.e. Zileuton, although that’s probably about 50% of the time. They often present with sinus disease, not always with nasal polyps and sometimes they have aspirin sensitivity, which is perhaps the most easily recognized specific asthma phenotype. The relationship to Th2 adaptive immunity has been unclear. While these patients are often less allergic and they have lower IgE levels they can have very high exhaled nitric oxide levels and clearly they have evidence of eosinophilic inflammation. So whether this has been a Th2 process or not has been unclear; but I think with some very recent studies that have targeted therapy, targeted Th2 therapy towards these individuals I think we realize that this is in fact a Th2 process as well.

So there are monoclonal antibodies that have been developed to IL-5. IL-5 is a cytokine that is a very pro-eosinophilic cytokine, which interestingly was studied in earlier, studied years ago in milder generalized asthma and there was absolutely no efficacy of an anti-IL-5 targeted approach in general asthma. But I think over the years we realized that well maybe only 50% of asthma has this eosinophilic inflammation, and when they targeted it to patients who had eosinophils it led to about a
40% reduction in asthma exacerbations in patients with severe eosinophilic disease. And if you looked at the age of onset for these patients most of these patients had a late onset towards their disease and they had associated eosinophilic asthma. But you can see that the placebo group exacerbated about twice as often as the anti-IL-5 treated group did in this particular paper.

Now late onset asthma also probably has an infection related component, and many later onset asthmatics actually report to you they never had asthma, they got an upper respiratory infection, it went to their lungs and they’ve had asthma ever since. And there has been an association of late onset disease with atypical bacteria, so mycoplasma, chlamydia with a paper reported now 10 years ago that showed that patients who had positive chlamydia titers and late onset disease had a greater decline in FEV1 over the years.

There was a study in mild moderate adult patients who were identified by PCR positivity for mycoplasma and they showed that those individuals who had PCR positivity for mycoplasma had a greater response to treatment with Clarithromycin as compared to those individuals who did not have PCR positivity, suggesting that there was a mycoplasma element in their airways that was responsive to a macrolide antibiotic. And then more recently in severe, mostly adult onset asthmatics with a mean diagnosis at age 29, there was an improvement in asthma specific quality of life following treatment with Clarithromycin, again this macrolide antibiotic; but interestingly no change in lung function.
Now there has been a lot of interest in neutrophilic severe asthma. Neutrophilic severe asthma has been described for many years, probably again a little bit in association with late onset disease, a little bit in association with high levels of corticosteroid use, smoking, etc. But when they actually looked in this study that was done in severe asthmatics for those individuals who had a neutrophilic type of inflammation they found that Clarithromycin actually decreased this neutrophilic inflammation, decreased the IL-8, decreased neutrophil elastase and actually achieved the best improvement. So a specific subset of late onset disease who had neutrophils seemed to respond better to this antibiotic approach as compared to, to the rest of the late onset group. And I think it suggests that this bronchitic neutrophilic type of adult onset may respond better to an antibiotic targeted approach.

So in conclusion, severe asthma certainly is a heterogenous group of syndromes and I think understanding the pathobiology of these phenotypes and syndromes can improve our treatment options even today, but as we move to the future linking phenotypes with genetics, genomics, proteomics will likely improve and personalize our treatment options for these difficult patients in the future. Thank you very much for your attention.