The last time I spoke at Grand Rounds, I talked about rare pediatric lung diseases and so today, I thought I'd just hit the opposite end of the spectrum and talk about probably the most common pediatric lung disease that we, or any of you see, and that's asthma.

So the learning objectives are fairly simple. Today, I'm going to tell you about some questions, some unanswered questions, in the diagnosis and management of pediatric asthma. And I'm not going address all the unanswered questions because there's thousands of them but I am going to address some that are actively being researched and specifically ones that are actively being researched here at Wake.

And the dual purpose of that is to try to give you a better sense of the clinical research that's going on here at Wake, the pediatric aspect of which I'm really trying to build up and want to get support and buy-in from other faculty members, from residents. And so I really want to let you know the depth and breadth of what's going on here at our institution.

I will be discussing clinical studies of the off-label use of medications in children. In fact, a lot of the asthma medications we use in kids under 12 are being used off-label.

And I should just note that Wake Forest University Health scientist does receive funding from the NIH, as well as some drug companies, AstraZeneca and Roche/Genentech to participate and conduct some of the studies that are being discussed today.

One final disclaimer is that I did a lot of my lit searching this week during the government shutdown and so it's possible, however unlikely, that some of these questions have been answered in the last week and they just haven't updated Pub Med yet. So if that's the case, feel free to submit your complaints to me and we will refund the price of admission.

With that being said, the first question I'd like to address, and I sort of put this in here kind of tongue in cheek as an unanswered question, but it really is a question that we maybe have only partially answered and that is what is asthma?

If you look back historically, there are descriptions of respiratory disorders that sound consistent with what we now call asthma from the ancient Egyptians. And they had some herbs that they used to treat patients with these symptoms.

As with most modern maladies, if you look back, somewhere Hippocrates wrote down the symptoms of this disorder.

The name actually comes from the ancient Greek word aazein, which apparently, first appeared in*The Iliad*. It means to gasp or take a small or final breath. And I did confirm this with our local Greek scholar, Dr. Constantacos and she helped me with my pronunciations. So I hope, if she's here, that I got that right.

No historical discussion would be complete without a reference to Sir William Osler and he wrote down an excellent clinical description of what we now call asthma. He did note that he thought it was likely related to a neurotic affectation. So I think that's a little bit of an interesting twist on things and I think, sometimes, that's probably the case but that's not part of our modern understanding of the pathophysiology of asthma.

And then one of my mentors in residency said, basically you can sum up a definition of asthma in about seven words. And it's a clinical syndrome-- or eight words-- a clinical syndrome of chronic reversible airways obstruction. And I think that simple definition holds pretty much true in most cases.

And so, as we know, when your airways are nice and open, air gets in. You can get oxygen in. You can get CO2 out. Everything flows nicely. But with asthma you have-- primarily starts with a thickened inflamed airway wall, mucus hypersecretion, and this leads to spasm or contraction of the circumferential smooth muscles of the airway that act to acutely contract the airways, making it difficult to move air adequately in and out of the lungs.

So what does the US government define as asthma? So I thought we'd look at the NHLBI guidelines, and these are paraphrased.

They say that it's a chronic inflammatory disorder of the airways. Includes inflammatory cell infiltration. Airway inflammation and infiltration contributes to airway hyper-responsiveness, airflow limitations, respiratory symptoms, and disease chronicity. So so far, this is fairly consistent with the short definition that I gave you.

Atopy is the strongest identifiable predisposing factor. I think most of us could probably buy that.

Viral respiratory infections are one of the most important causes of asthma exacerbation and certainly this is true in pediatrics.

But you do see some different clinical presentations and ask, well, is this asthma? Is that asthma?

So what if asthma symptoms are only related to exercise? Sometimes we call that exercise-induced bronchospasm because we don't want to label it asthma because it doesn't have some of the other features.

What if it only is related to viral illnesses and there's no clear signs of atopy? We see this in a lot in our younger kids. They get recurrent wheezing episodes with viral infections but do fine in between episodes.

What if the patient can't perform pulmonary function tests and you can't demonstrate that they have reversible airways obstruction? Well, that's a common problem in pediatrics. So we often have to rely on a therapeutic response to trials of asthma medications and that's fraught with difficulty because we're relying a lot on history that's inherently subjective.

What if chronicity hasn't been clearly established? Again, this is difficult to do in children because they haven't been around as long.

What if cough but not wheeze is the primary symptom? People have talked about cough variant asthma but if you don't have that wheeze can you really call it asthma?

So I think what all of this gets to is that there is a fair amount of heterogeneity in what we consider to be the asthma phenotype. And this is a point of interest among asthma research is to try to define subtypes of asthma because the thought is that maybe there are different phenotypes of asthma that will respond differently to different therapies. Maybe the disease course of these different subtypes is different and maybe we need to stop thinking of asthma as this big broad category and focus a little more on specific characteristics associated with different types of asthma.

So there's two ways to look at different phenotypes within something as broad as asthma. And one is a univariate, sort of hypothesis-based approach. And what this does is this identifies a particular aspect of the clinical presentation and sort of classifies the asthma based on that factor.

So age of onset-- is this early onset asthma, later onset adult asthma? Is it atopic, non-atopic asthma? There's a lot of work looking for biomarkers and using that to differentiate different types of asthma.

There's a lot of interest in whether inflammation in certain types of asthma is primarily eosinophilic or whether it's neutrophilic and the thought is that perhaps these are caused by different mechanisms and may respond differently to different therapies.

And then, response to therapy, I mean, we don't see it as much in pediatrics but there is this entity of steroid-resistant asthma. And then we've got more steroid responsive asthma. And is the steroid-resistant asthma really asthma because what we know about asthma says it should respond to steroids?

So that's one way to think about it, and it's somewhat simplistic but it is a good starting point.

Another way of thinking about asthma phenotypes that's recently emerged-- and some of the interesting early work in adults was done here by Wendy Moore-- is to use a multivariate approach and look at combinations of factors and using what's called a cluster analysis.

And so what this does is uses a sort of a complex statistical algorithm to evaluate however many data points you want to give it about an individual and group subjects within your cohort based on similarity across a wide range of variables.

So this involves more looking at complex characteristics. This is less hypothesis based. I mean, your hypothesis is that this algorithm will show you some subtypes but you don't really know what those are going to look like. You sort of let the data drive the clustering and so it's sort of a knowledge discovery kind of approach.

And as I mentioned, this has been done extensively in adults. Wendy Moore here did one of the seminal papers in the Blue journal. There have been others from the last five years. Anne Fitzpatrick, who's one of our colleagues at Emory who works closely with us, did a cluster analysis of severe asthmatics in children. There's another one recently published in the *European Respiratory Journal.*

And then, since I've been here, we've been working on yet another one of these. We drew our subjects from a consortium called the EVE Consortium. And this is a group of investigators who have performed genome-wide association studies in asthma and have pooled their data to sort of do additional larger analyses and you can see Wake Forest is in with some of these other big name institutions where a lot of great asthma research is going on.

And what we did was took 942 asthma subjects drawn from a number of different asthma clinical trials and used-- the algorithm decided there were nine standardized predictors that best divided these patients, these subjects, up into clusters and what we got was five clusters.

And so these are sort of hard to describe because there's no sort of one particular thing that makes them stand out but when we sort of roughly group them into severity, we can see there we get one group that's fairly mild asthma. These tend to have early onset, tend to have more normal lung function, and interestingly, we have minimal African-American representation in that cluster.

The more mild to moderate is the second largest cluster. A little later onset. These are more atopic, have a low normal baseline lung function, are predominantly Hispanic.

The mild to moderates have a little ager onset, higher BMI. Interestingly, they're the least atopic group and they are predominantly non-Hispanic, white, and African-American. So not many Hispanics in that group.

The severes have early onset, tend to be heavily male predominant, more atopic, and have the lowest baseline lung function.

And then the severes have high rates of hospitalization. This group is highly predominately African-American, have the highest BMIs, high levels of atopy, and the earliest onset and longest duration.

So I show you this not to say that this is the gospel or this is the way the five groups of asthma shall henceforth be known, but more to just give you an idea of different ways of thinking about phenotypes.

And that is something that we'll have to validate in another population but we want to look at whether certain genetic variants predict cluster assignment and whether there are other things that we can infer from this particular clustering approach.

The phenotype of severe asthma is one that's of particular clinical importance because it's associated with a lot of morbidity, sometimes mortality. If you all were it Catherine Cleveland Gilbert's talk, talked about some cases of fatal asthma that we've looked into. And the NIH is very interested in looking at severe asthma.

We are now in the third iteration of what's called SARP, or the severe asthma research program. And Wake Forest has been involved in SARP one, two, and we're now involved in SARP three, and this is largely on the strength of our adult asthma program, the leadership of Drs. Bleecker and Meyers, Dr. Steve Peters, Dr. Wendy Moore, really built a really strong phenomenal adult asthma research program here that has brought in a lot of NIH multi-center trials that I'm going to tell you more about in a bit. And we're really trying to get in on that and try to ride those coattails and make Wake Forest also a preeminent pediatric asthma research center.

So SARP is a group of seven clinical centers and one data coordinating center. The first two iterations of SARP were cross-sectional studies, so we saw patients at one point in time.

The really exciting thing about SARP three is it's actually going to be longitudinal. We're going to follow patients with severe asthma over two years. We're enrolling patients aged six to 75 years, although here, we're only doing age 11 and up.

As I mentioned, it's a two-year observational study. It's going to be exploring genetics, biomarkers of severe asthma, and seeks to really better define the phenotype of severe asthma in children and adults.

So we talked a little bit about what asthma is, the different ways that asthma can look. Another question that we have some information about but it's certainly not completely answered is what causes asthma in children?

And it's, as you would imagine, it's multi-factorial but one thing, one answer may lie in the Th1/Th2 system.

OK, so you have these Th null cells and they can go one of two ways. They can get exposed to bacteria and develop into Th1 cells, stimulate macrophage, go off and fight infectious diseases, all the stuff that Dr. Givner loves to talk about. Or if you don't get a lot of infectious diseases, especially bacterial infections, you get more exposure to viruses, allergens, you develop more of what's called the Th2 response.

And this involves some important interleukins I want you to pay attention to because they're going to come up again. IL-5, IL-13, and this leads to more of an antibody response and more of an eosinophilic type of inflammation. And this is the type of inflammation that we think is really important in pediatric asthma, although Th1 may play a role as well.

And there's some interesting data if you look at the geographic distribution of where asthma is that sort of plays into this. Asthma is pretty much a disease of the developed world. It does exist in developing countries but the rates are far higher in more westernized developed countries.

In the US, asthma prevalence ranges from about 5% in Idaho to about 13%, these are mean levels, in the District of Columbia based on 2009 data.

Highest prevalence of asthma is in developed westernized countries, the UK, New Zealand, Canada and the US all are among sort of the top countries in terms of asthma prevalence.

Prevalence lags but is increasing in developing countries as they become more developed and more westernized. Interestingly, South Africa, which is generally considered to be the most westernized country in Africa, on the continent of Africa, actually has the highest asthma prevalence rates on that continent.

So what accounts for these differences? Well, there's probably differences in diagnosis rates to be taken into effect. Genetic differences may play a role and certainly environmental factors are thought to be highly significant in the development of asthma.

So taking a break from hygiene, another thing that we do in developing countries that may be related to the development of asthma is we use a lot of acetaminophen or paracetamol, depending on where you live. And there's a lot of epidemiological evidence that suggests an association between increased acetaminophen use and development of asthma.

So far, this has all been really just sort of associational. It's been somewhat difficult to establish cause and effect relationships but the evidence does seem to be mounting.

This is an editorial, a very excellent editorial, written by Dr. John McBride in December of 2011. There have been other ones since then. There's a good review in the most recent issue of *Pediatric Respiratory Reviews,* but I like Dr. McBride's paper because he really lays out his argument.

One is that evidence is shown, in his opinion, a strong association between Tylenol or acetaminophen use and development of asthma. That this association has been consistent across age, geography, and culture. That it shows a dose response relationship. So we're sort of checking off those causation criteria as we go here.

He mentions the timing of increased acetaminophen use and the asthma epidemic, as well as the relationship between per capita sales of acetaminophen and asthma prevalence across countries. That may be confounded by other things. I mean, I think countries where they use more acetaminophen are probably more developed countries, but we'll grant that as part of the evidence towards this argument.

And he cites a double blind trial of ibuprofen and acetaminophen for treatment of fever in asthmatic children, as well as the biologically plausible mechanism of glutathione depletion by acetaminophen in the airway mucosa.

So as I mentioned, there's plenty of sources of possible confounding here to take into account. You can have confounding by indications. You could say asthmatics experience more viral illness, therefore they probably use more acetaminophen and so it's not really the acetaminophen that is driving that association.

There could be reverse causation in that asthma causes symptoms that result in more acetaminophen use or preferential use of acetaminophen by children prone to asthma over other analgesics. I mentioned some of the possible confounders with the epidemiologic data.

But the real question you all probably want to know is what do you do? So do you recommend not using acetaminophen for any children? Well, it's probably the most commonly used or one of the most commonly used drugs in our population. Is the evidence really strong enough to make that recommendation?

Secondly, it requires a very high degree of vigilance. I mean, even if they don't take children's Tylenol, you know, so many of the preparations that we tell people not to take but we know they still probably do contain acetaminophen.

So do you recommend not using acetaminophen in children with asthma or at high risk of developing asthma? Well, this is the approach that Dr. McBride-- this is not our Dr. McBride but the Dr. McBride that wrote this article advocates. Or do you await more conclusive evidence.

Well, if you chose three, hopefully, we will soon be able to help you out with that because one of the trials that we're currently enrolling for here is called AVICA and that stands for acetaminophen versus ibuprofen for children with asthma.

So this is not looking as much of the development of asthma in unaffected children but looking at whether acetaminophen use affects the severity of asthma in children with already diagnosed asthma.

It's enrolling children between one and six years old with mild asthma, sorry, that's one and five years old with mild asthma. And they will be randomized to either acetaminophen or ibuprofen in a blinded fashion as their as needed anti-pyretic analgesic.

The outcome that will be measured is asthma control days. So that's basically annualized days in which they report no asthma symptoms, no rescue inhaler use, and this is being conducted in conjunction with a second protocol that I'm going to be describing for you in a little bit here.

And this is being done through AsthmaNet, which is a large multi-center network funded by the NHLBI, is now in year five out of seven, a multi, multimillion dollar undertaking here. And you can see there are 11 partners, but within each of those partners there are multiple sites.

So for instance, we, as a site, are partnered with Emory. We used to be partnered with the University of Virginia but we're actually going to be entering into a partnership with a practice in Florida. So many of these partners have multiple sites.

You can see a lot of the major players in asthma research here across the country and it's nice to see Winston-Salem up there among those.

So what AsthmaNet is primarily focused on, whereas SARP is more of a sort of observational study, AsthmaNet is really focused on interventional trials, therapeutics. So these can be proof of concept trials. These can be comparative trials of existing therapies. And the real mission here is to find ways in which we can treat asthmatics, and in our case, children with asthma more effectively.

So just to give you a brief overview of asthma therapy, we have a number of different classes of medications that we use to treat asthma and the medications are really aimed at kind of the two aspects of asthma that I alluded to early on in the talk, the inflammation that sets the stage for bronchospasm and then the contraction of the airway smooth muscles that leads to acute bronchospasm.

So short-acting beta agonists relax that contraction of airway smooth muscles resulting in a sort of immediate relief of bronchospasms. And so that's what we use as a rescue therapy. That's when you have your most acute symptoms, we have you take your albuterol your levalbuterol, whatever your short-acting beta agonist may be.

Inhaled steroids are the mainstay of maintenance therapy really in asthma. And these come in a number of different preparations. They come as dry powders. They come as metered-dose inhalers. And the idea there is that you deliver the steroid right to the airway mucosa, right where it's needed and hopefully, bypass systemic absorption so that you don't get all the untoward side effects of systemic steroids.

As we know, there's some data that suggests that maybe even inhaled steroids can have some effect on growth in children. So this is something, I think, as pediatricians were acutely aware of, finding that balance between getting good asthma control and trying not to overdo it with the steroids so that we affect growth.

Leukotriene receptor antagonists, Singulair is probably the most commonly used one that you all are familiar with, is another therapy that we sometimes employ.

Long-acting beta agonists, such as salmeterol. There's been a lot of data and controversy about these that I'm going to get to in a bit. But these are used in combination with inhaled steroids and provide more long-acting bronchodilation in a similar manner to the short-acting beta agonists but with a longer duration of effect.

Oral/systemic corticosteroids, we try to avoid those as much as possible but often we'll use those to treat, especially, asthma exacerbations.

And then less commonly used therapies, anti-IgE monoclonal antibodies, which is omalizumab, or Xolair, is given by injection.

Mast cell stabilizers, such as cromolyn, very rarely used anymore. And a class of drugs that act in a similar manner to the leukotriene receptor antagonists but act on 5-lipoxygenase, which is one of the enzymes in the leukotriene response.

So we've got quite a bit in our arsenal. How do we go about deciding what to use?

Well, we turn to the asthma guidelines and this is taken from the 2007 NHLBI guidelines. And this is how we classify asthma severity and initiate treatment. And they have guidelines for zero to four, five to 11, and 12 and up. So I just picked five to 11.

So the first thing you do when you're assessing a patient, sort of new onset asthma or who hasn't been treated is you want to get an idea of the severity of their asthma and that is done by looking at both the impairment and the risk.

So impairment looks at factors. And these are all historical factors, in general, such as how many daytime symptoms, nighttime symptoms, how often they're using their rescue inhaler, and whether their symptoms are interfering with their normal activity.

Now, lung function is nice if you can get it. We rely on that pretty heavily in our clinic. I hear that, I guess, DHP, you guys have a spirometer and there's some use of that.

I think one of the most important things in using lung function in pediatric asthma assessment is really making sure you have a tech that knows how to coach kids because this can be highly affected by technique.

So if you get good data it can be very useful. If your data are somewhat questionable, it can cloud the picture. And I'm not suggesting anything about any particular lab, just it's important to make sure that your techs really know what they're doing with respect to doing spirometry in children.

And then the element of risk is sort of a new concept, but this, you'll see kind of changes whether you're assessing whether to start a therapy or step a therapy up or down. And this really assesses the severity since the last exacerbation, the relative annual risk of exacerbations, and factors that into how aggressive to be with your asthma therapy.

So once you've determined, based on this, which step, step one, step two down at the bottom, step three or up, then you go to the appropriate table and look for that particular age group and what are the recommended therapies.

And then, once you've started one of those therapies, one of the keys to asthma is re-assessment and re-evaluation. So you bring the patient back and now you are assessing control in a child who's already on therapy. So you're looking at a slightly different table.

And now in the risk column, the risk of reduction in lung growth is in there. So that's something you want to consider, as well as treatment-related adverse effects, and that is wrapped into your assessment of symptoms, nighttime awakenings, interference with activities, short-acting beta agonist use.

So this really makes you look at the balance between risk and benefit of what you're doing in terms of treating this patient's asthma.

So one of the questions that's come up is how do you know which one of these therapies to pick? I mean, sometimes the guidelines give you an option.

So let's say you have a patient in step two and they're a six-year-old and you want to step them up to step three. So it says preferred either low dose ICS or LABA, leukotriene receptor antagonists, or theophylline.

So you can just blindly pick one and see if that works but one of the questions is is there a way that we can-- and that's often what we do, but one of the questions, is there a way we can predict which patients are going to respond to which therapies so that we get that guess right more often than not and get more effective therapy, better asthma control sooner?

So this is a question that's actually been researched. And anybody who came to the Journal Club that I did will recognize this trial. And I'm constantly talking about the BADGER trial, but it's a really cool trial. I think everybody should be aware of it.

So this was published, hard to believe, a little over three years ago now. It was published by some investigators at Wisconsin, hence the name BADGER, but that stands for the best add-on therapy giving effective response.

So what they were looking at is when you have a patient that's step two and you're stepping him up to step three, is there any way you can predict which of those three options the patient's going to respond better to?

So they looked at six to 17-year-old asthmatics that were uncontrolled on 100 micrograms of inhaled fluticasone twice daily. And they used a really cool, innovative study design in that it's a triple cross-over.

And we can do this in asthma therapy because we have equipoise about how these therapies work. There's also short half-life so we don't need very long washout periods. This also allows you to try each subject on each of the three therapies, which reduces your sample size and allows each individual to act as their own control in two arms for the third arm.

And so the three arms were step-up of inhaled corticosteroids, addition of a LABA to inhaled corticosteroids, or addition of montelukast, or Singulair.

And the main outcomes they looked at were asthma controlled days, forced expiratory volume in one second, and acute asthma exacerbations.

And interestingly, what they found was it didn't break down exactly one-third, one-third, one-third, but every patient, every subject responded optimally to one of the therapies but there was no real clear indication how to predict which subjects would respond to which therapies.

There were some sort of mild suggestions that possibly a higher score on the asthma control test predicted better response to addition of a long-acting beta agonists. White race also seemed to predict better response to long-acting beta agonists versus black race.

If you look, the bottom graph shows probability of best response and probably the LABAs come out a little bit on top but certainly there are patients that responded more optimally to increased ICS or to the addition to leukotriene receptor antagonist.

So this is interesting. The way I take this is that LABA is maybe your best bet but if you've got a reason not to add a LABA, one of the other options is probably fine. Try that but always reassess. And if that doesn't work, try another one because sometimes you will get an optimal response. And what this suggests to me, is that if you keep trying, at some point, you're going to hit on a combination that works.

Now, of course, if you have to step them up beyond that, that's something you have to take into consideration.

And this is a study design that you're going to see is now coming up more often and more commonly in asthma studies, this sort of triple cross-over.

So we traditionally think of inhaled corticosteroids as being something that you have to take every day or they're not effective. But the flip side of using inhaled corticosteroids is the concerns about decrease in linear growth.

So question came up, could we use inhaled corticosteroids on an as needed basis in children? And at first, that seems kind of like asthma blasphemy but if you-- say you had a patient that's step one, maybe not quite step two, maybe not quite ready to put them on a daily ICS or they're on a daily ICS. They're doing really good and maybe you want to step them down but you're not quite ready to just take it off altogether, could you use that on an as needed basis?

And where I see this coming up a lot is in these kids that have viral-induced exacerbations and they're totally fine the three or four months in between. And they have another viral-induced exacerbation and then they're fine again for another three or four months.

And you'll often feel like, do I really need to be committing them to this long-term inhaled steroid therapy if really the only time they wheeze and have symptoms is when they get a viral infection?

So Dr. Martinez in Arizona and colleagues, recently published in *The Lancet* what's called the TREXA trial. And this stands for treating children to prevent exacerbations of asthma.

And so they looked at mild persistent asthmatics between ages five and 18. And they compared the daily inhaled beclomethasone use, which is what we usually do with daily QVAR versus rescue use, which is they only use it in conjunction with their albuterol. So whenever they go for their albuterol, they also

Take two puffs of the beclomethasone. And what they found was ICS plus albuterol, the PRN use was more effective at preventing exacerbations than albuterol alone and that linear growth decreased in the daily ICS arm but not in the PRN arm.

So they suggest this is possibly useful step down therapy for those step twos as you're moving into step one, to think about. And I've started using this somewhat in my practice as well.

So considering that, considering that inhaled steroids may be able to be used on a PRN basis in children five and up, what about in younger children?

So we look at the asthma guidelines for ages zero to four. And again, step two, the preferred controller medication is low dose ICS or alternative is Singulair.

Well, there's another protocol. This is the one that's being done in conjunction with the AVICA, where they're being randomized to acetaminophen or ibuprofen. And this is looking at three different step two therapies for children ages one to five with asthma.

And I have to say, this is the-- this is what happens when a committee gets to name a study. They call it INFANT but it's actually-- infants are excluded from this study. It's actually a study of toddlers and that's what the T in INFANT stands for. But that's what it's called.

And so what it is, or it's another double-blind triple cross-over placebo controlled study of children one to five with recurrent wheezing. What it's looking at is daily ICS, a daily inhaled corticosteroid versus leukotriene receptor antagonists versus as needed ICS and LABA for symptoms.

And each subject gets randomized to one of these to start and then, after a period of 16 weeks, there's a two-week washout period and they get randomized to the second. And so every subject will complete each of these arms and it will be looking at overall, does one of these therapies stand out above the others?

And then also on the individual level are there anything we can point to that might help us predict, again, as with the BADGER trial, which subjects are going to respond optimally to which therapies.

So this, again, is really getting at that notion of personalized or individualized medicine and really trying to use data to pick the right therapy the first time around.

And this just shows you the INFANT protocol with the addition of the AVICA. So these patients, in addition to this, if they consent, will also be randomized to get either ibuprofen or acetaminophen as their PRN medication.

Subjects are allowed to be in the INFANT part without the AVICA but you can't be in AVICA without INFANT and we are currently enrolling, recruiting, for this at Wake Forest.

So possibly one of the most controversial questions that's come up with regard to asthma therapy is the safety of long-acting beta agonists. And a lot of this stems from a trial called the SMART trial that was published, the preliminary results were published in *Chest* in 2006.

It was looking at salmeterol versus placebo in asthmatics older than 12. And the results that were published were just the preliminary results because it was actually stopped early for increased death among subjects who were just receiving salmeterol. Now, remember, these patients were not receiving combination ICS/LABA, they were salmeterol versus placebo.

And it was a small but statistically significant increase in deaths, 13 out of 13,000 in the salmeterol group versus three out of 13,000 in the placebo group. And most, if not all, of these were actually African-American subjects. So a lot of concern came up about the use, the safety of the use of long-acting beta agonists, especially in African-Americans.

Since that, a lot of criticisms have come out. People have said compliance with inhaled corticosteroids was not closely monitored. You know, subsequent meta analyses have not really shown this but the fact is the data are out there and people are going to be concerned about them until we can sort of refute these data.

As a result of this, the FDA issued black box warnings for LABA and the American Academy of Pediatrics came out with recommendations that LABAs always are used in combinations with inhaled corticosteroids. They suggest trying other options first. So the AAP would probably have you increase your ICS or add on Singulair before you add that LABA on and wean off as soon as possible.

And that's consistent, I think, with what the asthma guidelines say. I mean, they do say you're always reassessing and you always want to step down therapy whenever possible.

But it still puts that question out there and I think makes some people uncomfortable prescribing LABAs to especially African-American patients that are poorly controlled.

Five years later, the FDA decided we need to try and put this question to rest, We need to try and answer this with a randomized clinical trial. So the FDA mandated that all makers of long-acting beta agonists conduct trials to assess the safety of a LABA/ICS combination versus ICS alone.

So they asked for multinational, randomized, double-blinded, real world trials with each one of these medications with the outcomes being asthma-related deaths, intubations, and hospitalizations.

Huge, multimillion dollar undertaking on the bill of the drug companies, I might add, which is appropriate. The problem is we're not going to have those results until 2017 so we're going to have to decide what to do between now and then.

But there are going to be four-- there are-- as far as I know, these trials are all enrolling, four trials in adults and adolescents greater than 12 years old. They want to get in each of these trials at least 10% of the subjects less than 18. And each one of these is going to have about 12,000 subjects. So they'll have in total about 49,000 from these. So a lot of statistical power to detect these rare events, hopefully, if they do occur differentially.

Now, remember this is with ICS and LABA versus ICS alone. So there is not an arm of just the LABA alone.

And there is one study in children four to 11 and they're looking at Advair diskus and there's 6,000 subjects in that one.

Dr. Steve Peters, who's one of our senior asthma researchers and adult pulmonologists here, is the PI for the AstraZeneca Symbicort study. So we're recruiting children and adults, or adolescents and adults for that study here.

So as we get to the end of the talk, I've sort of talked to you about how do we use the therapies that we have optimally? A question that always comes up is what new therapies are on the horizon?

And if we look at the most recently approved asthma medications by class, you'll see other than Xolair, we really haven't had a new class of asthma medications in a while.

And Xolair is an omalizumab. It's an anti-IgE humanized monoclonal antibody that's given by injections, typically reserved for severe asthmatics with high IgE counts.

You can see that companies are still churning out inhaled corticosteroids. ICS/LABA combinations are still popular but it's really been since the late 90s that we really had a new class of medication, other than omalizumab, a new class of oral or inhaled medication.

And there's some interesting data looking at an old drug that's primarily been used in COPD but may have sort of second life as an asthma drug. This is looking at tiotropium, which is sort of a cousin of ipratropium. It's a longer acting anticholinergic given by inhalation.

And again, you can see a lot of Wake Forest names on this study. Dr. Peters is the lead author. Dr. Meyers and Bleecker, Wendy Moore, are all on this paper that came out in late 2010.

And this looked at using tiotropium for adults with asthma and found that, in addition to inhaled corticosteroid or glucocorticoid the tiotropium improved symptoms and lung function in patients with inadequately controlled asthma.

So we don't typically think about anticholinergics as being something that might be effective in asthma, but this suggests that it may be.

And in fact, there may be, in talking about different phenotypes of asthma, there may be a subset of asthmatics that are more responsive to anticholinergics as opposed to beta two agonists.

This hasn't been tested in children yet, so it's not really in use in pediatric practice. But it's something on the horizon that I think people are interested in investigating further in children with asthma and we may be hearing more about this in the future.

There is also a high interest in biologicals, thanks, in large part, to the success of Xolair. Xolair is a monoclonal antibody that binds up IgE. You remember when I talked to you about the T1, T2 response, IL-5, IL-13, were some of the most important interleukins involved in the Th2 response.

And there's a medication developed by GSK that's undergone some phase three trials and has shown promise. It's called mepolizumab. It's an anti-IL-5. This study looked at subjects age 12 and up and so this may be something that we see more studies on. This may be something that we see entering more into the pediatric practice, at least, for our adolescents.

And finally, there's a anti-IL-13 antibody that's produced by Roche/Genetech called lebrikizumab and this has shown promise in adults.

There is a study that is just starting to look at this in asthmatics who are uncontrolled on at least two controller medications. And we are applying for IRB approval and hope to be recruiting for this, as well.

So I think the types of patients that will want to be in this trial are the ones who have sort of maxed out on traditional therapy who don't mind coming in and getting regular injections.

But you talk to somebody who's taken all the medication they can, taking lots of oral systemic corticosteroids and often, they're looking for another option. So hopefully, some of these studies will provide drugs that we can use in those patients that don't respond to the rest of the drugs in our armamentarium.

So I just want to acknowledge my colleagues, my mentors, at the Center for Genomics, Dr. Meyers, Dr. Bleecker, Dr. Peters, Dr. Moore, Vic Ortega, and Greg Hawkins, Dr. Abramson and Dr. O'Shea for their mentorship.

Our Cloverdale research center, I don't know if probably most people don't know where that is. If you come down Miller Street, down the hill like you're coming to the hospital, make a left, right there on the corner there's a Goodwill truck. And just to the left of that is sort of a low-lying building. I think it used to be a Family Dollar or a Jiffy Lube or something.

It's actually a very nice clinical research center, where asthma research studies are conducted. We've got exam rooms. They do adult bronchoscopies there. There is a nurse practitioner, several coordinators on staff. They manage tons of asthma and COPD clinical trials.

Cheryl Wilmoth is helping me get our pediatric asthma research initiative going and we're trying to kid friendly up some of the spaces, get some brighter colors in there, get some snacks.

The good news is we're going to be moving over to Piedmont Plaza and so hopefully, we'll have an even nicer facility there and can really do more to kind of make that more of a kid-friendly space and help continue to establish ourselves as a big pediatric asthma clinical research center.

Colleague at Emory University, Anne Fitzpatrick, is a pediatric nurse practitioner who has done some phenomenal work in pediatric asthma and has helped me along getting our program going here.

Certainly AsthmaNet and Severe Asthma Research Program funded by the National Heart Lung and Blood institutes.

And be interested in people's thoughts about how we can promote asthma clinical research in our community here at Wake Forest but also in kind of the broader Winston-Salem triad region.

So with that, I'll stop talking and let you guys do some talking. So thanks.