[MUSIC PLAYING]

MARC C. GAUTHIER: Hi, I'm Marc Gauthier. I'm an assistant professor of medicine at the University of Pittsburgh in the Division of Pulmonary Allergy and Critical Care with a special focus on asthma. I'm going to be talking with you today about updates in mild to moderate asthma in 2020. I don't have anything to disclose. And so with that, we'll just jump in.

So there have been a lot of big updates in asthma over the last couple of years, a lot of excitement around the use of novel biologics in severe asthma and interesting findings in terms of asthma pathogenesis and origins of asthma. But there actually have been some really interesting and important updates in mild to moderate asthma over the last two to three years as well.

And we're going to focus on three of those specifically-- new literature about the recognition of the problem of overdiagnosis and asthma, as well as how this affects asthma mimics, understanding the burden of asthma exacerbations, especially as it pertains to the mild to moderate asthma population, and finally, updates to the Global Initiative for Asthma Guidelines that reflect the new data on single maintenance and reliever therapy or smart therapy that's come out over the last couple of years.

So with that, we'll jump in. We're going to talk initially about overdiagnosis in asthma. So one of the real challenges for asthma in the clinical setting is the asthma is defined clinically by the characteristic symptoms of dyspnea, wheezing, and chest tightness. But these symptoms are often highly nonspecific for asthma and can be present in a lot of other conditions as well.

And so there are a lot of conditions that can really mimic asthma. And we think in addition to things like COPD, there are also things like heart failure, mitral valve disease, and pulmonary edema, interstitial lung diseases, that can have very similar clinical presentations and even similar exam findings in the office. And so, one of the big questions is, then, how many patients who actually have an asthma diagnosis really have asthma?

So one of the big studies that's looked at this in the last couple of years, it was a study by Erin, et al, that was published in the *Journal of the American Medical Association* looking at re-evaluation of diagnosis in adults with physician-diagnosed asthma. What the study did is actually pretty interesting. They used random digit dialing from 10 Canadian cities, recruited 701 participants with an asthma diagnosis. So they basically just picked up a phone, called random numbers until they found people with asthma who were willing to come in and be part of the study.

They used a protocol that we'll go through with serial methacholine challenges in attempt to rule out asthma to really understand how many of these patients really had an asthma diagnosis. They ended up recruiting 613 subjects that were able to complete the protocol, who were eventually included in the assessment, and they excluded from the beginning patients who were on long-term systemic corticosteroids or who were unable to provide satisfactory spirometry performance. All right, so that's an important caveat, really, to this study.

And this is the protocol that they used. And you can see it's a pretty in-depth protocol. So the initial visit, they get spirometry with assessment of bronchodilator response. And if they had a bronchodilator response, they consider their asthma to be confirmed. If they didn't, then they proceeded to do a methacholine challenge at their next visit. If the subject had a positive methacholine challenge, they considered their asthma confirmed.

If they didn't, they then had them half their inhaled corticosteroid dose, as well as stop their long-acting bronchodilators and discontinue anti-leukotrienes, brought them back again for another methacholine challenge. If that was now positive after withdrawing some of their medications, they considered the asthma confirmed.

And then the process repeats. If it's negative, they had them hold all of their medications and then come back for another methacholine challenge. And if that was positive, they considered their asthma confirmed. If that was negative, then they considered them to have no physiologic evidence of asthma. And then they did follow-ups at 6 and 12 months to confirm that they remained negative during that timeframe. So if you made it through that entire extensive protocol, they considered your asthma to be ruled out.

And what was impressive is that, actually, 33% of patients in the study had asthma ruled out by this protocol. And you would think that a lot of these people are probably people with just a historic diagnosis of asthma. They haven't been treated in years, so they have maybe an albuterol inhaler that sits in the medicine cabinet that they haven't used in a long time. And that was true for a number of these folks.

But 79% of the patients who ruled out, 161, were currently using an asthma medication. And of those, 71, or 33%, were actually on daily maintenance therapy for asthma that they were able to wean off of as part of the study. And significantly fewer patients among those who ruled out had ever completed spirometry, right? So they did a logistic regression looking at predictors to help identify who are these patients who they ruled out. They found those who completed spirometry as part of their initial assessment were much more likely to have asthma than those who had not, which really argued, in their minds, that objective testing was really critical.

So they found overall that asthma in this cohort was overdiagnosed at a 30% rate, which was consistent with other literature in this area, although smaller studies, that patients with an asthma diagnosis but without asthma were still using asthma medications at a relatively high rate and were actually able to wean off those medications successfully.

Patients who were ruled out for asthma actually underwent further evaluation by a pulmonologist, and they were able to identify alternative explanations for their symptoms in about 60% of patients. And so, importantly, the asthma diagnosis in these patients has probably been preventing further workup that led to the ultimate actual diagnosis. And finally, I think the study really emphasizes the importance of recognizing overdiagnosis in asthma and the utility of spirometry to really confirm an asthma diagnosis.

And another study that just came out this year in the *Journal of Allergy and Clinical Immunology* looked at the study and tried to then apply what the cost effectiveness would be of using, essentially, universal objective confirmation for asthma diagnosis in the United States. And what they did was they used modeling to assess the cost effectiveness of a protocol that involves spirometry and methacholine to confirm every asthma diagnosis in adults.

And so, they had a simulated cohort of 10,000 adults with asthma in the United States. And they determined direct and indirect costs, as well as quality adjusted life years, over a 20-year period, to really get a sense of how cost effective would consistent, objective testing for asthma be, in terms of both preventing cost to the healthcare system compared to the cost of testing.

And so the algorithm that they proposed essentially was a two-step algorithm, so a lot simpler. And again, it looks very similar to the one that we just looked at, just abbreviated, right? So an initial spirometry with bronchodilator response, if the patients had a bronchodilator response, they considered their asthma confirmed. If they did not have a bronchodilator response, they went to a methacholine challenge. And if the challenge was positive, they considered asthma confirmed. If the challenge was negative, they considered their asthma ruled out.

With that, using data from the literature, they've constructed a rough tree of what they think their positive and negative rates would be, based on the studies out there that have done similar protocols. And then they compared, at the bottom here, the current standard of care, which has about, again, a 33% false positive diagnosis rate for asthma and 67% true positive with their model that would effectively diagnose true positive asthma.

In this case, as you see on the top, either by initial spirometry testing or by methacholine testing or truly rule out asthma for patients who completed the entire protocol, recognizing that about probably 10% in their model of the people who completed the protocol might actually have asthma, but be falsely ruled out.

And then, using that with other data obtained to try to, again, assess quality adjusted life years and healthcare costs from literature review, they found that assuming an overdiagnosis rate of about 33%, they'd have a cost savings over the 20-year period of about $35 million, as well as a gain of 4,000 quality adjusted life years. Extrapolated to the US population as a whole, the savings was quite significant.

And they argued really that that savings outweighed the cost of this objective testing burden as part of an asthma diagnosis. And so, they really argued in this study-- and I think the data supports it-- that using objective testing in asthma is really critical both to ruling out patients who don't have asthma and facilitating further workup, as well as confirming an asthma diagnosis, and really, ought to be part of the initial workup for any asthma patient if they've never had spirometry done.

Next topic that we're going to talk about is the burden of asthma exacerbations. So asthma exacerbations are really critical because they're one of the drivers of asthma morbidity. They may play a significant role in loss of lung function and airway remodeling over time. But we really don't have a lot of data about the burden population wise and what the pattern's exacerbations are, especially amongst mild to moderate asthma patients.

So this is a study that came out in the *Blue Journal,* Respiratory and Critical Care Medicine, looking at exacerbation patterns in adults with asthma in England. And what these folks did is they analyzed electronic medical record data from England from the National Health Service. And they included subjects who had at least seven years of follow-up for asthma during the 2006 to 2015 period and ended up identifying 51,462 subjects that they included in their study.

And then they looked at exacerbation rates amongst these patients. And they basically defined an exacerbation as a prescription to prednisone or a patient who sought evaluation for asthma in an urgent care or hospital setting. And then they looked at how many years of the study did patients exacerbate. What they found was actually pretty interesting, that almost 2/3 of the patients never had an exacerbation over the entire study period. 24% had only one exacerbation over the entire seven years. And 12% of patients had greater than one exacerbation over that seven-year period.

So really a small number of patients accounted for the vast majority of asthma exacerbations. They then really broke these out by GINA step therapy at inclusion in the study. And what they found is a little bit surprising, if you look at it. But in the chart here at the right, the initial bar on the left are patients who had zero or one exacerbations. Then we see two, three, four, five, six, and then, finally, patients who had an exacerbation every year in the study. And not surprising, the patients on step six therapy were almost all frequent exacerbaters over the course of the study.

But interestingly, the numeric majority of the frequent exacerbaters were actually patients in step one and step two therapy. And you can see really that a decent number of patients who were on only step one, step step two, or step three therapy actually had exacerbations on a pretty regular basis despite having, presumably, relatively low day-to-day symptoms as the reason for their being on relatively low asthma therapy.

They looked at risk factors for exacerbations, and they found that older age, lower socioeconomic status, tobacco use, obesity, coexisting allergic rhinitis, and GERD, were all predictors for patients to have any exacerbation over the course of the study. Interestingly, they didn't find any factors that actually successfully predicted exacerbation frequency, with the exception being that nested case control studies show that the best predictor of future exacerbations was just whether the subject had had a previous exacerbation, basically, again, kind of confirming this idea that there are patients who exacerbate and, really, patients who, for the most part, don't.

But again, I think the real take-home message from this study is that the recognition that exacerbations, at least in this cohort, appeared to at least be somewhat independent of day-to-day symptoms and recognizing these patients on GINA step one, step two, step three therapy, who are having regular exacerbations, despite relatively good day-to-day function, are good candidates for increasing their therapy, right, to try to get them out of this frequent exacerbation pattern.

One of the other, of course, more topical things of interest right now is with COVID-19 and asthma and the big question as to whether asthma is a risk factor for severe COVID-19 illness. And this is, of course, highly relevant because we know that many other viral exacerbations tend to be experienced with a much higher degree of severity in asthma patients than in patients without pre-existing asthma.

And so, this study, published as a letter in the annals of the American Thoracic Society this year, really looked at the prevalence of asthma in COVID-19 hospitalizations. So what they did was they did a meta analysis of English literature studies that looked at the prevalence of asthma amongst patients who were hospitalized for COVID-19. They identified 15 studies to include. And then they went and got paired studies to assess what the local geographic prevalence of asthma was as best as they could assess it, to try to get a comparison.

And so, what you see here in this chart at the right across these 15 studies, we see that the prevalence of asthma in patients who were hospitalized with COVID-19 is shown with these black circles with error bars. The local population wide prevalence of asthma for these geographic regions is shown with the green triangle. And what they saw was that asthma prevalence in COVID-19 hospitalizations appears to be consistently across these studies at or below the local geographic prevalence in the community for asthma.

And when they look at the cumulative data, they then compared that to influenza, which they thought would be the best comparator infection, which shows, in the US, a prevalence rate of about 21% in terms of hospitalized patients with influenza who have pre-existing asthma. And they saw that the COVID-19 prevalence was across the total across all 15 studies, right? It's significantly lower than that 21% rate seen in influenza.

And this really suggests that asthma is actually not a risk factor for COVID-19 hospitalization or more severe COVID-19 disease, although it's important to note that there are some confounds that may play a role, right? It may be that asthma patients are also better at avoiding high risk situations. They may be better about social distancing and more aware of wearing masks, right, to ensure safety because of their fears and their prior experience with viral exacerbations of their asthma.

So some potential confounding there, but overall, the data certainly doesn't support an increased risk of severe COVID-19 hospitalization amongst patients with asthma, which I think is pretty reassuring for our asthma patients who have, at least to me, expressed quite a bit of concern about their risk.

The last topic that we're going to get to and actually spend I think a bulk of this talk on because I think it's some of the more exciting data, but with some more caveats to that data, is the arrival of Single Maintenance And Reliever Therapy, or SMART therapy. And importantly, this was often meant to take the idea that patients would have a single inhaler, both for maintenance and reliever therapy. But where this has really gone to is the idea of a single reliever only therapy for control of asthma.

This idea isn't new. It's been around for a while. And there was a prior study again in *The New England Journal* by Papi, et al, that looked at the use of rescue beclomethason and albuterol as a single inhaler in mild asthma, really trying to answer this question of, do asthma patients actually need to be on maintenance therapy? Because some of these patients actually do better with just as needed therapy.

They recruited 455 adults with mild asthma for a trial period of six months. And they did a six-month double blind, double dummy randomized control trial with four groups. All right, and so that means that patients got identical appearing inhalers, one with a placebo and one with drug, for the use of the trial. So they really had no idea which arm they were in. They did an initial beclomethasone run-in period for four weeks to assess inhaler use technique, as well as adherence.

And then patients were randomized to four groups. So they had an as needed combination therapy group, an as needed albuterol therapy group, a regular beclomethasone therapy group, so a standard maintenance inhaled corticosteroid, and then a maintenance combination group, or regular combination therapy. And these patients then proceeded on that therapy for a six-month period.

Interestingly, what they found was that the as needed combination therapy was actually superior to as needed albuterol. And then their study was not inferior to the other groups, right? So we see here in the Kaplan Meier curve at the right, the lowest group in the study is the as needed albuterol therapy in terms of exacerbation risk, right? So patients without any asthma exacerbation, as needed albuterol clearly does the worst. And all three of the other arms were significantly better outcomes than the albuterol-only arm for exacerbation risk.

Interestingly, while it looks like there's a little bit of separation between the other three arms, they really are all non-inferior to each other for exacerbation risk. And so what they found is that the as needed combination therapy was not inferior to both the maintenance beclomethasone and the maintenance combination therapy for exacerbation risk. And importantly, the as needed combination therapy arm actually had a lower total beclomethasone dose than either of the maintenance arms did. And so, the idea that they were able to achieve non-inferior control in terms of asthma exacerbation risk, they had a much lower total steroid dose.

So one of the challenges with that approach is the combination of an inhaled steroid without buterol meant that your beta agonist was really relatively short acting in that combination product and concern that you would have to use it relatively frequently to get the amount of beta agonists that you would need to control symptoms. But the arrival of formoterol, which is a rapid onset long-acting beta agonist, offered a new option to really assess this strategy, right?

So unlike the other long-acting beta agonist, formoterol has relatively rapid onset of action within about 5 to 15 minutes of dosing, compared to one to two hours for most of the other long-acting beta agonists. And so the idea is that a combination formoterol-budesonide product might be able to achieve some of the same findings that we're seeing with the inhaled steroid short-acting beta agonist product, but maybe with better symptom control.

So this study was a 52-week double blind, randomized control trial, looking at subjects with mild asthma 11 years of age or older. And they compare-- did initial run-in period with terbutaline only. And then patients were randomized, again, in a double dummy approach, to either a placebo twice per day, plus terbutaline is needed. Terbutaline was the short-acting beta agonist used in this study. Placebo twice per day, plus budesonide-formoterol as needed, or budesonide twice per day with terbutaline as needed, and followed for 52 weeks. And they had electronic diary and an inhaler adhere its monitoring during that period.

What they found was very similar to the findings from the prior study, right, that very clearly the arm that used only a short-acting beta agonist did the worst in terms of exacerbation, right? So in the hazard curves at the right-- and again, the inset here is just blowing it up so you can really see the separation a little bit better-- we see that the terbutaline arm in blue clearly has higher exacerbation rates over the 52-week course of the study. And we see that the budesonide-formoterol as needed, as well as the budesonide maintenance group, overlap pretty consistently, in terms of their risk of exacerbation, both for mild exacerbations and for severe exacerbations, which shows, really, the same pattern.

And again, what we're seeing is that the as needed combination approach is certainly superior to as needed short acting beta agonists for preventing exacerbations and non-inferior to maintenance steroids for preventing exacerbations as well. Now they also looked at day-to-day symptoms in terms of how many weeks of the study were patients well controlled or what percentage of patients in each week were well controlled in this graph here on the right.

And what they saw here is that what was interesting is the maintenance group actually did better. So you see the budesonide maintenance group in gray here had a significantly higher percentage of patients with well controlled asthma each week of the study, whereas the combination product, as well as the terbutaline as needed arms, both were pretty similar, and they overlapped pretty significantly throughout the study in terms of symptom control.

And so, really, their conclusion was that both PRN therapies were inferior to maintenance therapy for day-to-day asthma symptom control. An important caveat, though, I think that you have to remember is that for the combination therapy arm, because these patients are using it on an as needed basis, they're waiting until they get symptoms to dose their inhaler. And so, that might confound this data a little bit.

And it may not necessarily be drug inferiority so much as the fact that patients are waiting until they're symptomatic to take their medication. And because of that, they're more likely to be symptomatic, the patients who are taking their medication on a daily basis, regardless of the presence of symptoms.

But overall, I think we can have the take-home point from the study that, clearly, combination therapy is superior to as needed beta agonist therapy alone, and that as needed combination therapy is not inferior to maintenance therapy for exacerbation risk, but, unfortunately, is inferior-- that the combination as needed therapy is inferior to maintenance therapy for day-to-day symptom control.

This study was paired with another study in the same issue of *The New England Journal* that looked at as needed budesonide-formoterol versus maintenance budesonide in mild asthma. In a very similar study designed, 52-week double blind, randomized control trial, subjects greater than 12 years of age with mild asthma. In this case, they were randomized again, twice daily placebo, and PRN budesonide-formoterol or twice daily budesonide maintenance therapy with PRN terbutaline. They ended up enrolling 4,215 subjects who were randomized between the two groups.

Then, again, we're seeing a relatively consistent pattern emerging here in terms of exacerbations, so probability of having a severe exacerbation amongst these patients. We see that again, maintenance therapy and be destiny for motor oil as needed therapy overlap pretty consistently on the hazard curve here. So really, the two therapies appear to be pretty identical in terms of their ability to prevent exacerbations within this asthma population.

Now looking, again, at some other markers of efficacy, they looked at spirometry, as well as symptoms. And what they saw here, again, this first graph is looking at change in pre-bronchodilator FEV1 from baseline. What we saw is that both groups actually had significant improvement in their FEV1 throughout the study, compared to their baseline. And for those who read a lot of asthma literature, this is not too surprising.

We know that there is always a little bit of a placebo effect in asthma research regardless, that just being enrolled in the trial improves asthma control and often improves FEV1 as well. So the fact that both groups improved, not too surprising. And again, some of that may also be due to the fact that both groups got inhaled steroids. But we see that the budesonide maintenance group actually does have a statistically significant, although a relatively small absolute difference improvement in FEV1 compared to the combination therapy as needed group.

And that improvement in the maintenance inhaled steroid group was maintained throughout the study when compared to the as needed combination therapy group, again supporting the idea that maintenance therapy seemed to be better for improving lung function over the combination as needed therapy approach, although both groups had significant improvements in their lung function over baseline.

Looking again at the effect on symptoms, which is, again, the other consistent finding that we've seen, and what we saw is that the change in asthma control questionnaire 5, which is a validated asthma questionnaire that assesses day-to-day asthma symptoms, they administered that test at each visit. And again, what we see is both groups have improvement in their asthma control by the ACQ5 score. And again, higher scores are worse here, and so reductions in scores would demonstrate improvement.

And we see that even as early as visit one, that the budesonide maintenance group is outperforming the budesonide-formoterol as needed group and that that significant improvement is maintained again throughout the entire course of the study, although, again, importantly, the absolute difference is relatively small between these groups. So while it is statistically significant, right, it wasn't really that dramatic of a separation between the two arms. So the degree of day-to-day symptom improvement for maintenance inhaled steroids may not have been all that much greater than that experienced by the as needed combination product group.

So our conclusions from this study, right, no difference in exacerbation rates between groups, right? So, again, as needed combination product was not inferior to maintenance steroids for preventing exacerbations, but that the as needed therapy approach was, again, slightly inferior to maintenance therapy for spirometry and for symptoms.

So we've seen a pretty consistent pattern emerge, right, in that the single maintenance reliever therapy approach, the as needed combination product with inhaled steroids, plus either a short-acting early on or later on formoterol, the rapid onset, long-acting beta agonist are superior to as needed short-acting beta agonist.

So they did better than albuterol, better than terbutaline for preventing exacerbations, that as needed combination in therapy was not inferior to maintenance steroids pretty consistently across all of these studies, but that the as needed combination therapy was inferior to maintenance therapy for symptom control. Although, as we noted before, part of that, again, may be due to the fact that patients are waiting until they're symptomatic to take their medication in the as needed approach. And so, that may confound that data little bit.

So the big study that came out last year that was pretty exciting for this therapy was a real world study published in *The Lancet* that really tried to assess the real world implications of this approach. And this is the budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline therapy, reliever therapy, in adults with mild to moderate asthma or the practical trial. This was a 52-week open label multi-center superiority randomized controlled trial that really looked to see, in a real world setting with open label drugs, how did these two approaches in therapy compare?

And so, what we can see is that, again, it's a real world design, open label randomized controlled trial at 15 primary care centers in New Zealand, recruiting mild to moderate asthma patients greater than 17 years of age, 52-week trial with two parallel groups, again, the as needed budesonide-formoterol versus a maintenance budesonide with as needed terbutaline.

And this should be a pretty familiar theme by now, but we could see here in, again, the Kaplan Meier curve at the right that the budesonide-formoterol as needed group in red actually outperformed the budesonide maintenance plus terbutaline group for exacerbation reduction. This is a number of severe exacerbations by percentage across the 52 weeks of the cohort. And so, again, definitely not inferior. In this trial, actually superior.

Although, remember, this is also a real world setting. So we'll get to a little bit later here some of the implications of that. But definitely, I think this is consistent with our prior data that combination therapy is definitely as good as maintenance inhaled steroids for preventing mild to moderate and severe exacerbations. And we began to see the same pattern here, moderate to severe exacerbations, the as needed combination product outperformed maintenance budesonide throughout the course of the trial for exacerbation reduction.

And again, consistent with the findings that we've seen before, the PRN combination therapy actually had a lower mean and median budesonide exposure. In this trial, almost half. And you see in the table here at the right in the middle, mean dose of 167 micrograms in the as needed group versus 302 in the maintenance group, median dose, again, 164 versus 328. So really, these patients were able to effectively half their total steroid intake without increasing their risk of asthma exacerbation on the whole.

They did have higher beta agonist use in the combination therapy arm, although, again, part of the caveat with that is that because these patients have a single inhaler, every dose of inhaler that they take has beta agonist in it, as compared to the budesonide maintenance group where, obviously, the maintenance budesonide doesn't contain any beta agonists. So that probably plays a role into why the combination as needed group had significantly higher beta agonist use than the maintenance group.

Now what's great about this trial is they also showed some subgroup analyses to try to really understand that while we're seeing this pattern emerge on aggregate, right, that combination product on an as needed basis is not inferior to maintenance inhaled steroids for exacerbation reduction, right, but may be worse for day-to-day symptom control, are there particular subgroups of patients that seem to benefit one way or the other?

And what they found is that, actually, two really important caveats emerged to their findings in this trial. And that when they looked at patients who had evidence of eosinophilic asthma, so patients who had an absolute eosinophilic count in this study of 400 or higher, those patients did significantly better on maintenance inhaled corticosteroids than on the as needed combination product.

And that, I think, is important to recognize and that patients with evidence of clear eosinophilic lung disease do better with regular inhaled steroid dosing. And this is consistent with a lot of the other data in terms of asthma phenotyping, right, that patients who demonstrate evidence of eosinophilic asthma, either in blood counts or eosinophils in sputum, tend to have a much better response to daily steroids than patients who don't. So it's not really too much of a surprise, then, that those eosinophilic asthma patients really did better on the maintenance therapy approach than they did on the as needed combination therapy approach.

The other really interesting caveat to this trial is that the other, while it didn't reach statistical significance, it was very close. A predictor for benefit was that there is a trend to significance for adherence and that patients who had greater ICS adherence did better with maintenance therapy. And again, this kind of makes sense when you think about it, that patients who are randomized to the maintenance arm, but weren't really great about taking their maintenance inhaled steroid didn't do that well in that arm.

And I think that really argues to what the overall benefit of this strategy is and that patients who just aren't great with inhaler adherence-- which admittedly is pretty hard to do, a twice a day inhaler, and all the literature would support that a lot of asthma patients actually aren't great about their adherence, especially in a real world setting, and that clinical trials often overestimate adherence-- that those patients do better with a medication that they can take on an as needed basis anyway. Because it more matches how they're actually using their inhalers.

So patients with low adherence seem to do better with an as needed combination inhaler approach. Patients who are really adherent with their medications trended towards doing better with maintenance inhaler approach. Again, I think that makes sense when you think about it. But I think it really supports how we use this data going forward. And so, all of this data led to the Global Initiative for Asthma to update their guidelines. And so a couple of big changes in the 2019 edition, right?

Step one and step two therapy had been changed to reflect this new data on SMART therapy approach. And so, now, the old recommendation for albuterol as standalone therapy has been completely removed from the Global Initiative for Asthma, given that, again, right, we saw time and time again throughout these studies that the short-acting beta agonist as needed arms always did worse in terms of exacerbation risk.

And so, that is no longer a recommended approach for mild intermittent asthma or step one therapy. The current recommendation is now as needed inhaled corticosteroids with formoterol, again that combination inhaled product. And again, the emphasis is that the formoterol is really key because it's a rapid-acting, long-acting beta agonist. Salmeterol is not going to get you that same rapid relief that formoterol is able to provide.

Now they recognize the recommended alternative then in step one is now as needed inhaled corticosteroids with a PRN short-acting beta agonist. So it'd be a two inhaler strategy with the probably somewhat unrealistic, if you're being honest, expectation that patients would take both when they're having symptoms. And again, I don't know that that's a realistic expectation, but that's sort of the recommendation now in that step one group.

And then the new recommendations for step two are, again-- so for your moderate or your mild persistent asthma-- is as needed inhaled steroid with formoterol combination with the-- so the exact same as step one, with the alternative being a maintenance low dose inhaled steroid with an as needed short-acting beta agonist.

The other big change that we didn't discuss today simply is more relevant, I think, to the moderate to severe asthma population, is that the recommendation for steps three through five has been changed to now recommend combination inhaled corticosteroid and long-acting beta agonist products over monotherapy with an inhaled steroid in those patients. And that reflects data that's come out of the multiple studies that the FDA requested that the drug manufacturers do, looking at risks for asthma death in combination therapy versus steroid monotherapy.

And those studies overall appeared to show a benefit towards exacerbation reduction with a combination inhaled steroid long-acting beta agonist over monotherapy with just an inhaled steroid at the same strength. And so, based on that data, the Global Initiative for Asthma also updated steps three through five to reflect the recommendation that combination products should now be the backbone of care on the main strategy arm. And monotherapy with inhaled steroids should be considered an alternative therapy in certain patients.

There are some big challenges, though, I think to implementing this recommendation, right? ICS formoterol may not be available on all formularies. There is only one combination product in the US that has those two drugs. And so, you're really limited in your ability potentially to prescribe it, based on someone's insurance coverage. And also, formoterol does not have an FDA indication for acute asthma management. And so, right now, I think the FDA recommendations would be against this approach to asthma therapy.

That FDA indication is something that I think will likely come relatively soon. There are some applications pending with the FDA looking into that. But as of now, there is no indication of formoterol for acute asthma management. So that kind of limits your ability to use single inhalers or single combination inhaler as needed therapy as a treatment strategy for asthma patients.

So to kind of summarize what we've gone over so far, right, we talked about the GINA updates, the fact that combination therapy with inhaled steroid and formoterol is now the recommended backbone for steps one and two, that ICS long-acting beta agonist is now the recommended backbone for steps three and up. But understanding that challenges remain with implementing this approach to step one and two with FDA approval and formulary availability, hopefully, that's something that's going to change over the next couple of years. But at least, as of now, that's going to be a challenge.

We talked about the increased recognition of exacerbations, that a small number of patients tend to concentrate the most exacerbations, that patients can have frequent exacerbations without day-to-day symptoms, and that asthma severity can be under recognized in those patients who have relatively good day-to-day astham symptom control, but are still exacerbating frequently.

And we talked about the problem of overdiagnosis, again, remembering that about 30% overdiagnosis rate with asthma and that objective testing can really help to confirm or rule out an asthma diagnosis in patients who have never had testing done, and finally, understanding that ruling out asthma is really critical to moving on to identifying other mimic conditions that could be causing symptoms. Thank you very much for your time. I'm happy to answer questions now. And you can certainly reach me by email at the address below. Thank you.