Dr. Mariam Hanna
Hello, I'm Dr. Mariam Hanna, and this is The Allergist, a show that separates myth from medicine, deciphering allergies and understanding the immune system. The art of medicine involves many skills, but one of its foundations is developing a strong differential diagnosis. A well-thought-out differential helps guide the history, focus the physical exam, direct investigations, and even inform treatment trials.

During my training, the good old ABC mnemonic was my way to get through school, really. And when it comes to chronic cough, you either need a really good mnemonic or a really good method to make sure that you are covering your bases and have an appropriate approach.

Take my patient. I have a patient who has known asthma. He was on ICS and LABA and eventually was started on biologics for several years now. He's been doing quite well until, unfortunately, he started smoking.

His compliance with puffers also dropped. I had initially blamed this and his new smoking habit for his chronic cough. We worked on compliance.

He still had a chronic cough. Spirometry looked okay. Chest X-ray was normal.

I know what you're thinking. I can't get a pheno, though, so thank you for telling me, but I can't get it. And I'm working on getting a sputum, but I actually have no idea when that'll actually happen.

I'm left with this predicament. It's those moments that I miss rounds during training with a whole bunch of people standing around the patient's door and saying, what's the next best step that we should do as a team?

And today, we're going to do one step better. I'm going to bring you the expert on chronic cough, and he's going to explain to you how you approach the next best step and the ins and outs of the diagnostics, the red flags, the pitfalls of the management of chronic cough. It is my absolute pleasure to introduce today's guest to you.

Dr. Imran Satia is a Respirologist and Associate Professor at McMaster University and really requires no introduction. He holds the Canada Research Chair in Chronic Cough, ladies and gentlemen. He is a respiratory clinician scientist with an expertise in chronic cough.

Dr. Satia completed a Master's in Neurophysiology and a PhD in Neuronal Mechanisms of Cough. He has always loved cough. He was awarded the British Medical Association James Trust Award.

He was awarded the European Respiratory Society Marie Curie Global Fellowship Award and the E.G. Moran Campbell Early Career Award and the ERS Mid-Career Gold Medal Award. Dr.

Satia has also developed a McMaster Cough Severity Questionnaire for use in clinical trials. So this man understands chronic cough.

It is my absolute pleasure that you said yes. Welcome to the podcast and thank you for joining us today, Dr. Satya.

Dr. Imran Satia
Thank you very much for having me. I think this is my first ever podcast, I might admit.

Dr. Mariam Hanna
You will do fantastic. So let's first come up with our basic definitions. Chronic cough. How do we define it clinically in patients?

Dr. Imran Satia
Sure. So the current guidelines recommend and state that chronic cough is a cough which is lasting greater than eight weeks. And this is basically in all commas.

So I make the differentiation between chronic cough and refractory chronic cough. So chronic cough, imagine that patient who's come through your door, who's been coughing for 8, 10, 12 weeks and hasn't had any investigations, no trials of treatment, nothing. And that's what chronic cough is.

After you've investigated, if you found any treatable traits or underlying conditions and you therefore then treat that condition and then despite treatment of those underlying conditions and traits, you still find that the patient has ongoing cough, then it's at that point that we call it refractory chronic cough. So that's the difference. So chronic cough is the initial, refractory chronic cough is after you've tried and failed and things are still not great.

There is another diagnosis called unexplained chronic cough is when you investigate and everything's normal and you can't really find anything treatable. Then we call that unexplained chronic cough and some guidelines have just merged it into one calling it refractory and unexplained chronic cough.

Dr. Mariam Hanna
Okay. And so different types of chronic cough or refractory chronic cough and unexplained.

Dr. Imran Satia
Yeah.

Dr. Mariam Hanna
What are the referral patterns that you see coming into your office for chronic cough as a respirologist? What tends to be the patient journey that brings them to you?

Dr. Imran Satia

Yeah. So just to give you a brief, I, we run a tertiary kind of level chronic cough service at McMaster. So probably half of my referrals are from other specialists like yourself, allergists, respirologists, even gastroenterologists, ENT, and about the other half are directly from general practitioners.

On average, these people have been coughing for about five to eight years every day for the last five to eight years. Often it's predominantly two-to-one ratio females to male. It tends to peak in the 50s and 60s.

But having said that post COVID, I'm seeing 30 year olds and 20 year olds presenting with chronic cough. So there has been a bit of a change in the demographics. When we measure their coughs, just to give you an example, using cough monitoring devices, on average, they cough around 20 coughs per hour.

On average, if you look at the whole population, that's 500 coughs per day, every day for the last five to 10 years. So you can now imagine that if you're coughing that many times a day, you're going to get urinary incontinence, sleep disturbance, fatigue, exhaustion, refraction, syncope, presyncope, social difficulties, work life problems. All of these symptoms you're going to develop because the fact that you're coughing 20, 500 times a day, sometimes more.

Dr. Mariam Hanna
Fair enough. And I told you about my mnemonic. But what's your approach?

Dr. Imran Satia
So the first important thing is I think it's very important for patient-physician interactions that you must validate that they've had this serious condition which is significantly impacting their quality of life.

So that's my first step that I do. Then I take a detailed history. I ask them a lot of questions about what kind of a cough is it?

Is it a dry cough? Is it a productive cough? How severe would you say the cough is on a scale of zero to 10?

Where do you feel it? What kind of sensations do you get? What are your triggers?

Hot air, cold air, strong smells, perfumes, aerosols, talking, laughing, singing, bending forwards, lying down, foods. How does it impact your quality of life? Work life, social life, family life.

So I take a detailed history. I look for other comorbidities and other symptoms and then what I'm trying to understand is that and red flags is important. I don't want to miss cancer, TB and rarely we seem to get a lot of patients also with interstitial lung disease and pulmonary fibrosis as well which is also an important thing we must exclude.

But often all of these things can help me to really understand number one, is this something serious? Number two, do I need further investigations?

And number three, are we really dealing with cough hypersensitivity syndrome and what we really need to do is suppress the nerves which I'm sure will come through later on maybe in the discussion what I mean by that.

Dr. Mariam Hanna
Okay so we've taken a really thorough history and then based off of your history my understanding is that we're going to direct our investigations kind of specific to that history or what you're being pointed at. We love our tests,and yes I understand like history is gold standard but you know I want to talk about reliability of some of the tests that we use in the evaluation of cough starting with the bread and butter spirometry if you don't mind. So in the evaluation of cough using your spirometry, how reliable is that?

Dr. Imran Satia
So I think there's three investigations which I think everybody must have, mandatory. Number one is the chest x-ray. Purely to give me some, it's not a test to give me some specificity but it's a sensitivity issue that if it's abnormal then it can direct me towards something like cancer or fibrosis or heart failure it could be for example it's also possible.

So a normal chest x-ray is reassuring. Then we do the spirometry. Now the spirometry again is there to demonstrate whether or not there's evidence of airflow obstruction, whether there's evidence of non-obstructive spirometry but a lot of the times it's normal.

So it doesn't really tell me what the diagnosis is if the spirometry is normal and even if it's normal that doesn't exclude asthma anyway but we do it out of a first pass to say is this normal. One thing I might want to add that many of our patients with chronic cough and refractory chronic cough they will struggle to do spirometry. So when you're doing the spirometry they'll say well as soon as I take a deep breath in I start coughing or sometimes I'm taking a forceful breath out I can't finish because I'm just constantly coughing.

It just triggers the coughing. So just be careful when you're interpreting the spirometry in a patient with chronic cough just look at the flow volume loop and look at the volume time graph to make sure that did they actually were they able to complete a good acceptable reproducible spirometry. But you're absolutely right it's sensitive but it's not a specific test.

It's not going to tell me what the diagnosis is. Very rarely I can look at a flow volume loop and I've got the diagnosis in one second and that is when you have somebody called tracheobronchial malacia where when they're breathing out on the flow volume loop you'll see this vibrating oscillation in expiration and from that I can tell OK this is likely tracheobronchial malacia. But that's very rare very rare very rare and often these people they have this barking

honking type cough and you can spot it from the waiting room so you don't even need a spirometry to diagnose that.

But so and then the third issue is the CBC. I think the CBC again if this, and we check it for the bloody eosinophil count typically right if it's elevated. But again it's not reliable because as we know you can have lots of people who've got normal bloody eosinophil and they've got asthma or normal bloody eosinophils and a high fetal and a high sputum eosinophils.

So it's not a diagnostic test per se but I would always recommend those three things everybody should have.

Dr. Mariam Hanna
OK this is very good. This is very important for me to hear. I want to introduce a couple of others.

Methylcholine like how often are you pursuing a methylcholine in these patients?

Dr. Imran Satia
Yeah. The reality is that because I'm at Mac I have access to methylcholine and sputum and FeNO in almost anybody I want. I'm a bit more judicious with doing that because I tend to think that if somebody has cough and do they really have wheeze and shortness of breath associated with it and independent of it.

And if it is then you know I will do a methylcholine challenge. The only caveat is that there is this cough variant asthma, which you may be aware of, where it's not classical asthma in that they don't have wheeze or chest tightness. The only symptom that they have is cough and they've got a positive methylcholine.

So I would suspect in my clinic if you were to audit it I suspect at least 90 percent have had a methylcholine challenge. Because I just want to know that is there any evidence of airway hyperresponsiveness and do I need to really try them with an ICS lab first before I try anything else.

Dr. Mariam Hanna
Oftentimes my methylcholines come back as borderline and I'm left with this like that's life. And then you know nowadays we talk a lot about FeNO mostly from guidelines but in the community access to FeNO is a struggle and not timely if I were able to ever coordinate getting it. So it won't help in my acute asthma patient but I often think like perhaps a phenol in my chronic cough patient may hel.

Is that so or what would you say?

Dr. Imran Satia

So I tend to I do I must admit I like using FeNO and the main reason why I like using it is because it's a point of care test. They come to clinic it's sat next to me in the clinic and I can just do it and within two seconds or two minutes I can provide it to do a sufficient blow and a good enough blow. I can get a decent answer of whether or not there's any evidence of a high FeNO and evidence of possible type two inflammation.

The only problem is what you do with that information. So there's a study that was done relatively recently published in Lung which randomized people on based and gave them ICS based if you had a high FeNO. If you had a FeNO more than 25 parts per billion you gave them ICS to see whether or not they cough got better and the reality is that only in about 50 percent did it get better.

So that doesn't really some would argue that you know you know just because you've got a high FeNO does that tend to tell you that they may have underlying that FeNO is a treatable trait and therefore you should give them high dose ICS or medium to high dose ICS. The jury is still out because we haven't got a proper prospective randomized controlled trial which is giving them you know ICS or a placebo based on a high FeNO. So we don't have that but I do think occasionally I've been detected FeNOs of 100, 150 and I've given ICS and they've had a response.

S o I'll often say okay let's do a phenol just at least this is something new and different which they haven't seen before and we've looked under every single stone and left no stone unturned as they say.

Dr. Mariam Hanna
And in the process of leaving no stone unturned I think I've already heard you speak about an ICS trial or an ICS-LABA trial. How often are you doing empiric trials if nothing is really pointing in a particular direction to?

Dr. Imran Satia
This is an important question. When I was doing with the ERS guideline task force on management of chronic cough a couple of years ago one important thing came out. I think one of the things I've noticed in Canada and also in the UK is primary care physicians and other physicians they like to just give empiric treatment of PPI.

Just give it as a first pass and actually what it's demonstrating is actually causes more harm and your benefit to getting it is only in those people who have at least some subjective symptoms of heartburn, indigestion, bloating, dyspepsia, these kind of symptoms. So they at least if only give it to those people who actually have some evidence at least subjective or objective evidence of reflux. Because if you just give it to everybody your yield is very low.

And then often once you start the medication it's very difficult to stop the medication. When it comes to ICS-LABA I only reserve it in those people who either have positive methacholine, a reversibility or they've got a high FeNo or high sputum. I don't give it empirically.

I don't. And often patients will tell you that actually taking the inhaler made their cough worse. Because particularly with the dry powder inhalers.

So if I'm going to give an inhaler I often will have tried to avoid dry powder inhalers and give them an MDI with a narrow chamber so they don't have to take those deep breaths in and out which might trigger their coughing. We already know that it's so difficult to take inhalers anyway and  if you've got chronic cough then it's even more difficult. So it requires a bit more education on how to take it.

So I try to avoid empirical treatments if possible at all.

Dr. Mariam Hanna
Point well taken. And I also like the, you know, the interest in that like PPI trials may be like overdone actually with more harm than benefit.

Um, I also trained at McMaster, so I want to talk about sputum and I want to know your true feelings about an induced sputum, real world use.

Dr. Imran Satia
It's a challenge. So I won't do it in everybody, I'll do it in my second round of investigations. If when I first take a history and exam, I feel like, well, it could be, this could be that let's do these things. And then after they come back and they think, okay, we've tried this and it hasn't worked.

And I still think that there's some evidence of eosinophilic bronchitis or in some cases neutrophilic bronchitis. I have a lot of patients who have mild bronchiectasis, not overt bronchiectasis, but mild bronchiectasis. And in these patients, I want to know if there's evidence of neutrophilic bronchitis.

And I also send sputum culture to see if they've grown any bugs. So in these people who've got a bit of bronchiectasis, I will try them on low dose macrolide azithromycin. So my sputum is informing me, am I going down a neutrophilic route?

Am I going down an ICS route? Or am I going to give a bit of both? Is there a sputum bug that I need to treat?

So it can be very helpful in those refractory chronic cough patients. It's not always helpful in the chronic cough patients, but in the refractory chronic cough patients, it can be very helpful.

Dr. Mariam Hanna
OK. And I think it's really important to talk about cough hypersensitivity syndrome.

Let's talk about that because you brought it up and it's already causing me some hypersensitivity as we're saying it.

Dr. Imran Satia
So cough hypersensitivity, we've kind of felt known about this for many decades, actually. And the first thing I'm going to say is that this is more of a clinical syndrome. And the easiest way to describe this is that there's excessive coughing to low levels of thermal, mechanical or chemical stimulation.

So thermal, mechanical, chemical. So the first thing to understand is that all human beings, they need to cough. Coughing is very important.

It's the archetypal airway defensive reflexes. Human beings didn't have cough would have been a significant problem. So we need cough to protect our airways.

And this is exactly what I say to patients. We need cough to protect the airways. And how coughing is initiated is that the lining of our throat and our lungs are lined by these tiny little nerves, which are branches of the vagus nerve.

Vagus nerve comes from the brainstem. And the job of the vagus nerve is mainly, particularly to the trachea and lungs, is a sensory element. It senses what's going in and out.

And when something activates it, an action potential, electrical activity gets generated and it goes to the brain and it tells the brain, OK, something is there. And then it's up to the brain to decide, shall I act on this or shall I ignore this? OK? Now in cough hypersensitivity, and all of us have at some point in our lives felt that, like, you know, you'll feel a tickle, you'll feel an urge to cough and eventually you'll just cough.

Now, what we've discovered in refractory chronic cough is that this pathway of the sensory nerve, the brain processing, has gone wrong. So we think either the peripheral nerve is acting up and is firing off when it doesn't need to fire off, or that the brain, when it's receiving the signal, instead of ignoring signals which are harmless and saying, don't worry about it, this is harmless, it's considering them as harmful and it's telling the body, cough, danger. OK? That's what we're dealing with.

Dr. Mariam Hanna
Are there red flags or non-respiratory causes of cough that should never be missed?

Dr. Imran Satia
So things which I don't want to miss are things like cancer, TB, interstitial lung disease and heart failure. You know, those are four big things which I don't want to miss because those are otherwise treatable and need specific therapies. The other thing which I'm seeing a few rare cases these days are some rare genetic conditions where people come to me presenting with things like peripheral neuropathy, sensory neuropathy and dizziness and some cerebellar signs.

And I've seen two cases recently of what we call CANVAS syndrome which is cerebellar ataxia, vestibular ariflexia syndrome with chronic cough. This is a genetic condition with RFC in the RFC1 gene and this triplet repeats, excessive triplet repeats. The sad reality this is a progressive neurological condition.

We can't do anything about it. But the point is that they need treatment and they need monitoring. They need supportive care, conservative care.

So I don't want to miss anything neurological. I don't want to miss somebody who's aspirating and coughing because of aspiration. And I'm often worried about people with strokes, MS or anything neurological and, you know, which makes me wonder,  I have a low threshold for requesting videothoracoscopy and barium swallows to make sure I don't miss aspiration.

It's very important that you don't miss that.

Dr. Mariam Hanna
In the management of cough, if it persists despite many of the things that you have tried and we've talked about like many things, what do you do? Like, are you ever left with the chronic cough patient that is not responded to many treatments? There's no red flags.

Dr. Imran Satia
So, in my clinic, there's at least 60% who don't respond to anything or who have been to somebody else before and they've come to me and they've tried everything and failed. So, that's about 60% of my patient population. And what I do in these people, I have, first of all, I explain to them their condition.

Often patients are just relieved when I tell them you have a disease. It's a neurological disease. We call it cough hypersensitivity syndrome.

And therefore you need treatment targeting nerves. That's a simple message. And then I said to him, we have four options and I'm going to suggest to you we try the first one first because the evidence is strongest for that.

And that is, we should first try you on low dose morphine, sulfate treatment, just five milligrams twice daily. It's a very safe dose. It's very effective at that dose.

It's not going to cause you addiction withdrawal at this dose. And what I actually do is I do a two week test first. So, it's like a two week, that in and of itself is a trial or a test.

And I just say, just take this for two weeks. I want to ring you after two weeks. If the cough doesn't get better, then you'll know about it.

And if the cough does get better, you'll know within three or four days. It can be like a switch, a light switch. And it just suddenly goes away.  And we do get these people, super responders,

So, that's the pathway for those people who are responders to morphine. If they're non-responders, then I, second line, I would go to pre-gabalin or gabapentin. Pre-gabalin, I would normally start at 50 milligrams twice a day for a week, then go to 75, then maybe 100, but I'd never go more than 150 milligrams twice daily.

Or gabapentin, 100 milligrams, three times a day, 200, 300. The doses that were used in the studies were actually much larger. So, gabapentin, they used 600 milligrams three times a day, which are industrial doses, which I've never, ever prescribed.

Pre-gabalin, I've given 150 twice a day max, never more than that. And the fourth line, if everything else fails, and particularly in those people, if they've got a history of depression, I tend to bring forward amitriptyline and try that 10 milligrams at night or 25 milligrams at night slowly and see how that goes. There's another treatment option which I use, I'm quite fortunate, is non-pharmacological cough control therapy and speech therapy.

So, we do have some local speech therapists who've shown some interest in managing patients with chronic cough. So, I do send patients to them, they have a four to five week online or virtual or even sometimes face-to-face sessions, and these are all designed to teach people how to suppress their cough and how to avoid triggers. And there's no reason why you can't do it along with pharmacology as well, particularly in those people who've had a partial response to pre-gabalin, gabapentin, and they need a bit more extra help, then you could try that.

Dr. Mariam Hanna
And sorry, if I may ask, treatment duration. I heard it clearly for morphine trial and who's going to be the responder or not.

And I understand that you titrate up the dose, but like how long of a trial to say if you're a responder or not for the other ones?

Dr. Imran Satia
For morphine, you'll know within a week. For pre-gabalin or gabapentin, normally six weeks, six to eight weeks, you should get some signal. So, it does take a bit longer, but if it is going to work, you should know within six weeks.

And then what I tend to do at six to eight weeks is I phone them and decide whether or not, are they tolerating it okay? Should we go up? Should we go down?

Should we, you know, and often patients will tell you that, oh, I've had benefits, but I'm happy to stay here or I want to go down a bit and just see how we go. And the final thing which I didn't mention is that many patients, after, they would rather participate in clinical trials of new drugs because they feel like these are all off-label non-licensed treatments. So, I'd rather try something which is directed towards directly inhibiting the vagus nerve.

So, we, that's why we run clinical trials so that we can have these new therapies to see. And it gives patients access as well. It's important.

It gives people access to therapies which otherwise they wouldn't have access to. So, that's the other thing we do.

Dr. Mariam Hanna
Awesome. All right. Time to wrap up and ask today's respirologist, Dr. Imran Satia, for his top three key messages to impart to patients and physicians on today's topic, chronic cough. Dr. Satya, over to you.

Dr. Imran Satia
So my first important message is don't miss any important reflex as doctors. Second important message is that refractory chronic cough is a distinct neurophysiological disease. And number three, new treatments are coming.

And at the moment we're using neuromodulators and speech therapy.

Dr. Mariam Hanna
Thank you, Dr. Satia, for joining us on today's episode of The Allergist.

Dr. Imran Satia
Thank you for having me.

Dr. Mariam Hanna
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It helps others find the show. And remember, learn to define chronic cough and do a CBC with differential, spirometry, and a chest x-ray. I got it right.

Sincerely, The Allergist.