

Pulmonary Issues and OI

Dr. Robert Sandhaus

Tracy Hart: *Hello and welcome to the Osteogenesis Imperfecta Foundation's monthly podcast. My name is Tracy Hart and I am the CEO of the Osteogenesis Imperfecta Foundation. Each month, the OI Foundation brings you information about the diagnosis and treatment of osteogenesis imperfecta presented by an expert in the field of OI and rare bone disease. The podcasts are a part of the ongoing educational effort of the newly formed Brittle Bone Disorders Consortium, part of the National Institutes of Health's Rare Diseases Clinical Research Network. The professional education activities of the Brittle Bone Disorders Consortium are led by the OIF. Our podcast today will focus on Pulmonary Issues and OI.*

*We're very excited to have with us today **Dr. Robert Sandhaus** of National Jewish Health in Denver, CO. Dr. Sandhaus applies his experience with internal medicine, pulmonary disease, critical care medicine and the biopharmaceutical industry to the study of lung disease. Dr. Sandhaus serves as the Clinical Director at the Alpha-1 Foundation in Denver, CO and the Medical Director and Executive Vice President of AlphaNet. Dr. Sandhaus is also a member of the OIF's Medical Advisory Council and a former member of the OIF's Board of Directors.*

Welcome and thank you so much for being with us today, Dr. Sandhaus.

Dr. Sandhaus: I'm really glad to be able to be here today.

Great, so we're going to get right into our questions. My first question is, when we talk about having good respiratory health or healthy lung function in general, what are we talking about? I'm not sure people understand how our respiratory health affects our health in general – could you give us a brief explanation of that and maybe what types of terms that people will be hearing when they're having a lung function test or something.

Well, it's hard to talk about problems with the lungs without understanding what the respiratory system is made up of and does. Generally, we consider the respiratory system to include everything from the tip of your mouth and nose down through and to the deepest parts of your left and right lungs. The job of the lungs is to essentially put the outside world into contact with your blood. It does that so that it can exchange oxygen, get oxygen into the bloodstream so it can power all of the tissues of the body, and so that you can exhale carbon dioxide (or CO₂) which is a byproduct of the burning, if you will, of the fuels oxygen and proteins or sugars that you might consume to make your muscles work, make your brain work, things like that. There are lots of places where the respiratory system can get into trouble. Right from the nose-having a stuffy nose, having a sinus infection, things like that, down through the larynx (the voice box) which among its many functions is to make sure that food and water go into the stomach and air goes in and out through the lungs and never between shall meet. Except that sometimes never isn't actually the case and you can get things that shouldn't go into your lungs going into your lungs. Then there's the windpipe (or trachea) that brings the majority of the air down towards the lungs that branches like tree branches into bronchial tubes and eventually into air sacs that are little microscopic grapelike appendages on the very ends of the smallest bronchial tubes. That's where the work of the lung takes place. That's where the oxygen and the carbon dioxide get exchanged. Obviously, the heart is

an intimate part of the respiratory system because it's the organ essentially contained between the lungs that pumps that blood that needs to pick up oxygen from the right side of the heart, oxygenates it, then sends it to the left side of the heart where it sends that oxygen (well, oxygen is blood with its CO₂ removed) throughout the parts of the body. So you can see there are many places where activity is going on and unfortunately there are many places where this activity can fail. When physicians are looking to evaluate whether someone's lung function has been affected by disease, by injury, whatever, there are a couple of things that they rely on. They rely on, first of all, something people call PFTs (Pulmonary Function Tests) which can be as simple as an office spirometry. Spirometry is a test when you take a deep breath in, blast it out into a machine and that machine measures how much air you exhaled as well as how fast that air was moving out of your lungs. Those two measurements can be used to evaluate an awful lot about what's going on in your lungs. Of note, that does not actually measure how well oxygen is moving into your blood from your lungs, some of the more important things. It's a simple way to gain an overall picture of how your lungs are doing. Physicians may also get arterial blood gases to look at the actual levels of CO₂ and oxygen in the blood as well as what the blood acid base balance is. A simpler way to look at oxygenation is something called an oximeter, which you can put on a finger or an ear and it measures how well the hemoglobin in the blood is carrying oxygen away from the lungs. This measures as a percent of the hemoglobin molecules in the blood that are carrying oxygen. So by looking at those things, as a pulmonologist, we tend to first divide people with lung problems into two tabs: those who have restriction to the movement of air in and out of the lungs, and those who have obstruction to the rapid movement of air out of the lungs. So in someone who's restricted, that means that all the volumes (the volume you inhale, the volume you exhale) are all reduced essentially symmetrically. If you have obstructive lung disease, it usually means you can get air into the lungs well, but the exhalation of air is impaired. Just to give some examples, restriction can be caused by the lungs becoming too stiff for instances; the lungs have fibrosis or fibrous tissue building up on them so the lungs can't expand correctly. Obstruction is probably better known to people because obstruction to the exhalation of air can be caused by things like asthma, chronic obstructive pulmonary disease, emphysema, and chronic bronchitis, things that are damaging to the airways or the alveoli themselves as opposed to putting scar tissue in the lung. The thing that's often overlooked in thinking about the entire mechanism of respiration is that the thing that drives all of that air in and out is, of course, the chest wall and the diaphragm. The diaphragm sitting below the lungs moves up and down between the abdomen and the lungs and give you the inhalation and exhalation movement and then the intercostal muscles of the ribs allow the ribs to move up and down pivoting on the spinal column like a bucket handle to make the chest larger and smaller as you inhale and exhale. So anything that can affect anything from the tip of your nose to your abdomen to the bones of your rib cage can affect your lung function.

That was so interesting. I've learned so much in 5 minutes, that was great! We know through surveys that we've done here at the OIF and being part of the OI community that some people with OI have breathing issues and seem to be prone to respiratory illness from time to time, you talked about the mechanics there, could you talk about why this might be the case for people with OI?

The first answer is that obviously someone with OI can get any of the conditions that any of us could get. In terms of lung disease, if a person with OI is a smoker they can get chronic obstructive pulmonary disease like emphysema, chronic bronchitis, asthma is extremely common in the general population which means it can occur commonly in patients with OI. There are some specific issues related to OI and the respiratory tract. First of all, in people with severe OI, there can be fractures of the spine or fractures of the ribs that affect the chest architecture and the ability of the chest as an efficient bellows to move air in and out of the lungs. Patients with small stature can have more pressure on the abdomen pushing up against the diaphragms making it harder for the diaphragms to go for their full excursion to get air in and out of the lungs. Something that we're just coming to appreciate is the fact that we know that for many cases of OI the genetic defect is a defect of collagen synthesis mechanism. The body makes collagen, one of the main connective tissue building blocks of bone, in an incorrect fashion either because of bad collagen genes or bad genes on protein surrounding the collagen gene. That leads to the breakage of bones and the characteristic features of people with OI, but it's not as widely appreciated that collagen is the major connective tissue that makes up the lungs as well. The lungs have a very delicate architecture that allows these air sacs to expand and contract to bring the outside world in contact with the blood supply. Most of that architecture is made up of collagen fibers. It's kind of what holds the structure of the lungs together. Individuals who have certain types of OI can have not only derangements in the collagen in their bones leading to fragile bones, they can also have derangements in the collagen of their lung that leads to usually restrictive types of lung problems where they can't move air in and out as well as someone with normal collagen. If you add on top of that problems with chest architecture, someone might have kyphoscoliosis that collapses one lobe of the lung or the other that leads to a situation which says that you might inhale with every breath might tend to pool in parts of the lung where air isn't moving well. Bacteria that you inhale, instead of being rapidly moved out of the lungs through coughing through what we call the mucociliary escalator that carries things out of the lungs so you can swallow them or spit them out, it can lead to a situation where the lungs are actually a breeding area for infection because the lung is not able to clear those secretions and inhale particulates and bacteria as rapidly as someone with normal architecture can. It leaves patients with OI that have abnormal chest architecture and/or abnormal collagen in their lungs at greater risk for things like lung infection. Perhaps they're more susceptible to the effects of cigarettes than a normal individual would be and simply the fractures that can occur that affect the structure of the chest wall, whether it's kyphoscoliosis, fractured ribs can lead to impaired movement of air in and out of the lungs, and eventually impaired clearance of things from the lung. It's a complex picture that all seems to be working against OI patients who have problems with the connective tissues and bones of their chest.

So having said that, what can a person with OI do to prevent respiratory illness, in your experience?

Well, I think that the knowledge of having these potential issues is important. First of all, if a consideration is being made if your kyphoscoliosis is worsening and consideration is being made to treating the kyphoscoliosis, one of the elements in that decision-making process should be how the improving of kyphoscoliosis or preventing it from getting worse interacts with the lung disease. It may be that someone would say "well, it doesn't quite reach the right angle to be kyphoscoliosis, to be operated on now or stabilized now." If there's an element of pulmonary impairment, it might suggest

that that person would be pushed towards getting that taken care of. Clearly there are things you could do to keep your lungs in better shape. I guess the first thing that always has to be mentioned is, OI patients, as with anyone, but especially OI patients should not smoke. If they've started smoking they should really work on cessation. Family members shouldn't smoke around OI patients. I've talked to OI patients who say "it's the one joy I have in life, smoking this cigarette"... find another joy. Talking from a lung perspective. There are various treatments that people can do- there are clearance exercises people can do, respiratory muscle, strengthening exercises, weight loss (especially abdominal weight loss) can really help those diaphragms move better and clear things better. There are cough exercise you can do to clear secretions better. I have to say, probably the most important thing is to get evaluated by a physician and treated by a physician early if signs of respiratory conditions occur. For instance, if you have wheezing and shortness of breath when exerting yourself, head to a pulmonologist or an allergist who's experienced in treating to find out if it's asthma and get on the appropriate asthma medication. Usually bronchodilators, sometimes inhaled steroids-although that has to be considered in someone with brittle bones. If there's a history of COPD in brothers, sisters, etc., probably shortness of breath should be evaluated for those kinds of problems and there are therapies, COPD is treatable. The most important thing is to, early in adult life, get lung function testing because there are problems with testing the lungs of OI patients, especially OI patients with short stature. All of our lung function testing that are done on individuals that have normal stature is based on calculating a predicted normal for a given individual. That normal is calculated on very few things- your age, your sex, your race and your height. Height has the greatest impact among those things on what the baseline normal pulmonary function should be. With OI patients with short stature, if the predicted normal values are based on a person's actual height, you will underestimate the size that person's lungs should be. You may come back with results that say you are 120% of the predicted normal, you're super normal; your lungs are just fine. When in fact, the lungs are severely affected. So the way that we try to get around that is to not look at predicted normal, but to compare someone against themselves to get longitudinal lung function testing on a given individual. Get a lung function test when they're doing well, get another lung function test when you're doing well. See what direction things are going. Then, when you have a lung function test during an episode of shortness of breath or a problem that has been identified, you can compare it to the previous testing and know whether this is normal for you or represents an abnormal lung function test. You can often tell what type of lung problems a person is having by comparing to their lung function test when they were normal. There are some ways around the height issue. You can, instead of using height, use arm span, but the problem with arm span is if the person has had multiple fractures of the long bones, and has rodding or anything like that in their upper extremities, then arm span is not going to be an accurate substitute for height. The physician that's evaluating an OI patient has to take all of this into account and sometimes they need some help from the OI patient themselves to think of these issues in evaluating something. The tests that we do of oxygenation, like blood gases, like oximetry, are not affected by the things that affect pulmonary function tests. Someone having a low oxygenation or an elevated carbon dioxide level, that's the same implications for an OI patient as for any pulmonary patient and would be treated similarly. There is a whole regimen that we do for patients with any of these lung diseases to try to keep patients healthy. Those regimens include the same things for OI patients as we do for any potential lung patient. That includes prophylactic measures, like getting immunized against the flu every year; because the major impact of flu on the general population and

obviously on the OI patient are lung problems. Getting an influenza lung infection, or often a secondary bacterial infection with a severe case of the flu. OI patients should be considered in the group of patients who should get a pneumonia vaccine. Right now there are two different kinds of vaccines that are in the different types of bacteria that cause pneumonia. OI patients should get both types of those vaccines.

And Dr. Sandhaus, their physician would be able to tell them which vaccine they should get for pneumonia?

Yes, it would be very easy to prepare a card of something that would talk about that. Basically, there's the old type pneumonia vaccine, Pneumovax, which raises antibodies in the body, gets the sugar coding of the most common bacteria that causes pneumonia. That should be given early to anyone who hasn't had it. There should be a booster at 10 years after its been received. That's the one that's been around for years. The new ones are these PCV vaccines; Pneumococcal conjugate vaccines, they actually raise antibodies in the body against the proteins that make up these organisms. As far as we know, that only requires one injection in someone's life, although time will tell if that's the case. It can't be given within a year of when the other type of vaccine was given. It tends to get complicated, but those of us who see a lot of patients, kind of have it drilled into our head when that should happen. But if a patient isn't offered a pneumonia vaccine, they should know to ask for it.

Got it

The other things that I mentioned already, controlling weight, exercise to keep those respiratory muscles in good shape and having a physician who you can have a long term relationship with who will understand the changes that you might go through because it's tough to see someone with a rare disease and hear a complaint of shortness of breath and know whether that's new for them, even know what to do with it, if they haven't had a long term relationship. Unfortunately, the current healthcare system is very hard to maintain long relationships with physicians.

Right, right. This is excellent information Dr. Sandhaus. We only have a few minutes left, but I wanted to talk about quickly, do you recommend sleep studies for people?

Well, one of the things that we didn't actually talk about and it is a risk for OI patients again, especially those with short stature, is sleep problems. Sleep apnea, sleep-disordered breathing, these are very common issues in people who have anatomic abnormalities of their neck; short neck, thick neck things like that, which can often describe a severe OI patient. People that I've seen and physicians I've spoken to who follow a lot of OI patients find that sleep issues seem to be a major problem in severe OI patients. Doing a sleep study can identify what the mechanism is of someone's sleep-disordered breathing. Most of the time, it's what we call obstructive sleep apnea where the muscles in the back of the throat relax and that relaxation causes intermittent obstruction to the flow of air where someone actually stops breathing during the night. These kind of intermittent cessations of breathing are just the magnification of the normal resting respiratory actions to happen to anyone during the night. The difference comes when those apneic episodes come when you're not breathing get to be too long or deep. There are easy treatments for those; I guess I have to put "easy" in quotes. The things that are

difficult in an OI patient is number 1, becoming comfortable in a sleep lab that's not made for someone with stature issues. We always encourage our OI patients to bring whatever pillows, bolsters, whatever they use to sleep at home with them to the sleep labs so they can sleep in the same position that they sleep at in home. Number 2: most of the treatments for sleep apnea or things like that involve putting a mask on the nose or the nose and mouth and attaching it to a machine that pushes air into the lungs. Fitment of those kinds of masks can be a problem in some OI patients. In general, I've never found something that wasn't solvable in that regard. We should talk about supplemental oxygen if we have time to do that.

Yes, I think we just have a couple minutes left, absolutely. Then we're going to bring you back again because this has been so valuable, the information you're sharing. We can't thank you enough. So let's talk about that, and then we'll wrap up.

Great. So, one thing that someone with lung problems, whether they have OI or not, is often recommended is to go onto a supplemental oxygen line, called a nasal cannula, it's a tube with prongs that sits in the nostrils and goes over the ears and down to an oxygen tank or an oxygen machine of some sort. When that's recommended, it's an important medical treatment. It should be thought of sort of like a drug, because it is something you take that has a medical action. People with lung disease from OI, people with sleep apnea from OI, people with emphysema, with bronchitis, sometimes that condition gets so severe that they're not able to deliver enough oxygen to the body for the person to do the things they want to do. The first thing that supplemental oxygen does is it raises your oxygen level in your blood so that your muscles can work more efficiently and so you can do more and deliver more oxygen to muscles, heart and brain and keep them functioning up at peak efficiency. Sometimes even more importantly, there's a subtle thing that happens when the oxygen isn't arriving at the lungs in sufficient quantity. When the lung sees low oxygen levels, it has kind of a protective mode that it goes into. It shuts down the blood supply to the part of the lung that isn't getting oxygen. The blood supply can be shunted to the parts of the lung that are getting good air and good oxygen delivered. It should be a very efficient mechanism if the delivery of oxygen is impaired in one little part of the lung. But what if the entire lung is affected and the entire lungs arterial supply is shut down? That puts great strain on the heart and you can actually get something called cor pulmonale, which simply translated means "heart disease due to lung disease." Then you get something called secondary pulmonary hypertension because the pulmonary arteries start to constrict to keep blood from flowing to parts where there's no oxygen, and if that's the whole lung, that's not good and eventually the right heart can fail. The treatment for that is supplemental oxygen. If you get that oxygen up again the blood vessels relax in the lung, the right heart can pump blood through the lungs without impediment and that's actually reversible if caught early enough. So, supplemental oxygen and once someone is adjudged to need it, not only lets someone do more with the amount of lung function they have, but it also protects the heart from being strained and eventually failing. It can be a very important medication for people that have underlying lung disease.

We're getting the high sign Dr. Sandhaus. Thank you so much! We're going to have you back again because this was so great. You can visit our website at www.oif.org to find out more information. Dr. Sandhaus, thank you so much!

My pleasure.