15:48:07 DELIVERY OF MEDICATIONS TO THE LOWER AIRWAYS

15:48:07 SPEAKER: Michael Rock, M.D.

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15:48:47 DR. ROCK: Thank you, Ellen, for that introduction. It's a pleasure to be here this morning. With the title of today's talk, if you were expecting Whitney Houston to appear, I'm sorry to say that she could not make it, so I will be here instead.

15:49:02

15:49:02 This is really a very important topic, given that we deliver so many inhaled medications to the airway in children. I'm going to speak mostly about asthma, but of course I have an interest in cystic fibrosis and there are some unique challenges in CF patients regarding medications that are available to deliver to the lower airway.

15:49:21

15:49:22 I know probably many people come in with preconceived notions as to what is the best way to deliver medications to the airway. This might be controversial. We'll see in the next 40 or 45 minutes if the data that I'm going to show you might change your mind. I'll show you what's happening on a national basis with regard to medications delivered to the lower airway.
So the learning objectives are to describe the different delivery devices for inhaled medications, learn of systematic reviews of the use of nebulized medications versus metered dose inhalers and the treatment of acute asthma, and learn of the use of valved spacer devices with metered dose inhalers.

I do have one disclosure. I am a member of the Cystic Fibrosis Foundation Data Safety Monitoring Board. We monitor several studies, and in my role I'm paid a very small amount for my time with monitoring those studies, and I will reference off label use of medications during this talk.

So we're going to start with a case report. This is a real case. I did not make this up. This is someone that I saw in the spring of this year. When I saw him in clinic, he was an 8-month-old that had had quite a bit of coughing and wheezing. He had had three to four emergency department visits. He was already on nebulized Albuterol and Pulmicort at home, and this is a direct quote from my dictation to the primary care physician: "He wears a face mask, but the mother is finding it a bit more challenging to give these treatments. His
past medical history is significant, for last winter he was hospitalized here in our ICU with RSV and he required intubation and mechanical ventilation and he's had coughing and wheezing ever since then. The pertinent part of the exam was that he had audible expiratory wheezing and intercostal retractions. He had inspiratory and expiratory wheezing also on auscultation with a stethoscope."

So I stopped the nebulized Pulmicort and Albuterol, began Flovent 44 micrograms per puff, two puffs using spacer with a face mask twice a day. His intervention plan was Albuterol for puffs using spacer with mask as needed for cough or wheeze and repeat up to every four hours as needed. We received a phone call from the family five days later. He was doing very well. No wheezing. Very seldom coughing. So this is quite gratifying that in a very short time, this child that had audible wheezing when I saw him in clinic, he was totally clear by changing his modality of therapy from nebulized to metered dose inhaler. So there are certainly challenges in delivering medications to the lower airway. We have all
15:52:12 evolved to try to keep the external environment
15:52:16 from getting inside us, with the exception of
15:52:20 obviously we have to breathe air all the time. So
15:52:23 molecular oxygen, we want to get that down into
15:52:25 our alveoli, but particles bigger than oxygen,
15:52:28 it's not desirable. We have a torturous route in
15:52:34 the upper airway. You consider the hairs in the
15:52:36 nose, the nasal turbinates. The nose will filter
15:52:41 out particles that go down as small as 1 micron in
15:52:44 size. Even if one is breathing through the mouth,
15:52:46 you certainly have a torturous route to go beneath
15:52:49 the vocal cords with a 90-degree turn in the back
15:52:52 of the throat. And it's really thought that
15:52:54 breathing through the mouth particles of 5 microns
15:52:57 or larger are filtered out.
15:53:00
15:53:00 Once you get down into the lower airway, we all
15:53:03 know that the airway branches over and over and
15:53:05 over again. There is something call the Weibel
15:53:09 model of airway branching where there are 23
15:53:11 generations of airways, and each time there's a
15:53:13 branch point, that's a corner that medications
15:53:19 have to negotiate to get down to the target
15:53:21 region. In asthma we're certainly looking at
15:53:23 delivering medications to smaller airways down
15:53:25 here. The same could be said for cystic fibrosis.
15:53:29
About the only time I could think that you would want a medication in the upper airway would be a child with croup and giving them nebulized racemic epinephrine. You certainly want that to work right in the sublatic region right beneath the vocal cords. So our challenge in delivering inhaled medications to the airway is to defeat these filtering mechanisms that should keep out particles from the lower airway.

In terms of talking about particles delivered by medical devices, be they nebulizers or metered dose inhalers or dry powder inhalers, the way to characterize the size of the particles is called the MMAD, and that stands for median mass aerodynamic diameter. That is a central tendency of the size of the particles; in other words, 50% of the particles are smaller, 50% are larger. As we just spoke about on the previous slide, the upper airway of the nose, the larynx, the trachea, certainly with the upper airway most of those larger particles are filtered out. To go beneath the vocal cords, one needs particles of less than 5 microns in size, so the 2 to 5 micron size gets beyond the vocal cords into the airway.

Now, once you get into the airway, you have
different ways of particles settling on the airway. Particles that are greater than 5 microns, and sometimes those do get beneath the vocal cords, they can slam into these branch points. They can slam into walls. That is called inertial impaction.

Particles of 1 to 5 microns in size, those can settle on airways by sedimentation. In other words, it's by gravity. And the longer the residence time in the airway, in other words, if one holds your breath, that gives those particles more time to settle out. And in fact, there have been estimations that with a 10-second breath hold, that increases the amount of particles deposited in the airways by at least 10%.

And then lastly, a way that particles can settle on the airways, particularly in the respiratory region, is by Brownian diffusion. Those are really like molecular forces of these particles interacting with each other. You might, in fact, you would want Brownian diffusion if you wanted to get particles into the distal distal bronchioles, even alveoli. Let's say you have a patient that you need pneumocystis prophylaxis, but they're allergic to TMP sulfa. They can be on nebulized
pentamidine once a month. You'll want that to go
certainly as distal as possible, so you would be
relying on Brownian diffusion for those patients.

There are a number of factors that determine
erosol deposition. Those that can divided into
eosol factors and patient factors. As we just
spoke about, aerosol factors, the particle size
distribution is very important and generally we
say that the respirable range is less than
5 microns.

Aerosol density is important, also. If you have
many particles in close proximity to each other,
those can coalesce, and then they're not greater
than 5 microns in size anymore. There are
hydroscopic properties. It's a humid environment
in the airway, given that we warm and humidify the
air with the upper airway down at the lower airway
and particles can grow in size. And viscosity and
surface tension also play a role in the size of
the particles.

Just as important as the aerosol factors are the
patient factors. Inspiratory flowrate is
certainly important, and we'll see that in a slide
here in a moment. And inspiratory flowrate is
device dependent. With dry powder inhalers, which we will talk about later, one needs a very fast inspiratory flowrate. You need to de-agglomerate particles off of the carrier vehicle in dry powder inhalers.

That is in contrast to metered dose inhalers, where you want a slower inspiratory flowrate so that you don't have that inertial impact. You don't want the particle slamming into those branch points in the airway.

Title volume, respiratory rate, and breath holding time, those are all important in the hang time or the residence time in the airway, the amount of time the particles are in there that can settle out by sedimentation.

Certainly upper airway anatomy is important. If you have a toddler with large tonsils, they have a bigger anatomic challenge in their upper airway compared to a teenager who does not have large tonsils. Lower airway obstruction is certainly of issue. You can't get the particles to distal airways if there's quite a bit of obstruction.

And then lastly and very importantly, the ability
to use the device is key, and that goes with any device, be it nebulizer, dry powder inhaler, metered dose inhaler. There has to be instruction of the patient. This is not like writing a prescription for amoxicillin and saying, "Take this orally three times a day." There really has to be instruction of these different devices to families and to the patients if they're old enough to cooperate and understand.

This is an example of effect of particle size on distribution. This is nuclear scintigraphy of two different particle sizes. You can see with the 4.5 micron size over here on the left, there's quite a few particles here in the throat. There are particles that have been swallowed into the stomach. And you have some particles in the lungs, but it's more of a central airway distribution. Compare that to the 1.5 micron size where you have much more homogeneous distribution of the particles throughout the lungs. So particle size definitely makes a difference.

I mentioned flow rates earlier, and flow rates make a difference, also. This is the fast flowrate here on the left side, inhaling at 80 liters per minute. And again, it's more
central distribution of these radioactive particles, compared to a slower inspiratory flowrate of 30 liters per minute where there's more equal distribution of the particles throughout the airways. 

So the history of inhaled medications goes back to 2000 BC in India. And back in that time, there were herbal preparations such as the Datura plant that were used for medical purposes. The root of the Datura plant, Datura is Angel's Trumpets. It has alkaloids, which has potent anti-cholinergic bronchodilator activity. They took these roots, they crushed them up, mixed them with ginger and pepper, smeared them on a reed, which was dried, and then that was smoked. So that was maybe the first reference to inhaled medications in history.

The first time that the term "inhaler" was ever used was by Dr. John Mudge in 1778. He published a book called "A Radical and Expeditious Cure of a Catarus Cough." He proposed inhaling opium vapor through this Mudge inhaler. You can barely see on here. There are some holes right here in the handle of this inhaler. The patient puts their mouth on this mouthpiece here. They inhale. Air is drawn through these holes, goes through
16:01:23 bottom of this tankard, which is where the opium
16:01:26 solution is at. So this is the first reference to
16:01:29 the word "inhaler."
16:01:31
16:01:31 We go forward to more modern times and what's been
16:01:38 around certainly for many, many years is
16:01:41 compressors and jet nebulizers. And I brought one
16:01:44 here. People have seen this before, but I'll just
16:01:47 set this up here for a moment. We won't do the
16:01:49 whole treatment. A ice lime green. They don't
16:01:52 all come in a green color. Tubing, plug that in
16:02:04 here. We'll talk about different nebulizers here
16:02:05 in a moment. I just have some saline here. Twist
16:02:09 this off. I'll squirt that in there. If anybody
16:02:15 wants a saline breathing treatment this morning,
16:02:17 you can come on down and get your breathing
16:02:19 treatment. So it only goes one way. I just
16:02:26 discovered something. That kind of makes sense.
16:02:27 You've got this round part here. I tried to put
16:02:29 it in there. That wasn't work. So you've got to
16:02:31 go back this way. This round part is back here to
16:02:35 the handle. A mouthpiece, and we'll plug this in
16:02:43 here, and away we go. And you can see the fog
16:02:48 coming out of the mouthpiece there. It's a little
16:02:51 bit noisy, so we won't run it any further.
16:02:55
16:02:55 So what just happened there? What's the physics
or the physics behind this? When you have a gas source go through a small capillary tube, you have a high velocity right here at this outlet. There is one or two capillary tubes that go down into a reservoir. There's something called Bernouilli's law. When you have a high gas source going through an opening, there's a decreased pressure right there. That causes the liquid to be sucked up through this capillary tube and then there are shearing forces on the surface of that liquid that turn this into various particles of different sizes.

What is not shown in these schematics or these nebulizers is there are a series of baffles here. There's a huge spread of particles that were just developed when we turned on the compressor. They range in size from .1 to 30 microns. Obviously, 30 microns is a huge size. Inertial impaction, which we talked about earlier in the airways, that occurs in the nebulizers, also. Those larger particles impact against baffles in there. They rain back down to the reservoir and they get re-nebulized over and over and over again. That is the fate of 99% of the particles. So only 1% of the particles actually are output to the patient.
This is something called the mainstream nebulizer. Over here is something called the side stream nebulizer. That's actually a brand of nebulizer, and that's because the capillary tube comes in alongside the compressed gas source. You're sheering across a larger volume with this cross-section here, compared to this here. So these, in some ways, can be more efficient.

The problem is all nebulizers were not created equal. This was a study done at National Jewish Hospital in 1994. Each one of these numbers here has a different brand of a nebulizer. There's 17 available brands in the U.S. when they did this study. This shows time of nebulization to the point of eight-fold decline in particle output. The diamonds are the 95% confidence intervals. The horizontal line is the mean. And each one of these boxes is the average determination of triplicate treatments with four different nebulizers, but of the same brand. So they had four nebulizers produced by the same company. For example, number two here is the Acorn. They took four Acorn nebulizers. What's interesting is these three boxes here are together, but this one right here is quite different from those three, so
that tells you the manufacturing process of these nebulizers, even though they try to make them precise, there's variability in the output of these nebulizers.

The other variability you see amongst the different brands of nebulizers here, this one takes forever to get down to an eight-fold decrease in particle output. And you can see the other variability with the other brands of nebulizers. This is delivery of particles in the respiratory range in milliliters per minute. And again, you can see some variability. Some of the better nebulizer brands are this one right here. Number three is called the Aqua Tower. Numbers 12 and 13, this is the Peri-LC. Number 13 is a Peri-LC Jet Plus, which is the nebulizer that I had here. And number 15 is the Side Stream.

By the way, we're talking about brands of nebulizers. It looks like maybe the medical students are off today. I often hear on the wards people say, "A child got an Albuterol nebulizer." Grammatically, that is incorrect. It's Albuterol by nebulization. There's no such thing as an
Albuterol nebulizer. There is a Peri-LC nebulizer; there is an Acorn nebulizer; there's an Aqua Tower, but there is no such thing as an Albuterol nebulizer so just semantics here, but it's grammatically incorrect.

Because of this variability in nebulizers, the FDA requires on package inserts that in phase three studies, the recommended use of that medication is with a particular nebulizer and compressor that was done in the studies. In the case of Pulmicort, which was what the child was on in the case presentation, I don’t know what kind of nebulizer he was using. I think it probably would have been useless for me to ask the family, because they would not know, either. If you look at the package insert for Pulmicort, it says a Peri-LC Jet Nebulizer with a pericompressor. It also says that other nebulizer and compressor combinations have not been tested and safety and efficacy are unknown.

The other interesting issue about Pulmicort, that was an eight-month old infant that was on Pulmicort. I sent them a disclosure slide that I talk about off label indications in this talk. Pulmicort is only approved by the FDA down to 12
16:08:14 months of age. Certainly it doesn't mean that
16:08:16 it's necessarily unsafe, but it is an off label
16:08:20 use of Pulmicort.
16:08:21
16:08:22 There are certainly many, many challenges in
16:08:24 nebulizers. I plugged it in before everyone got
16:08:27 here. I connected the tubing. I put the
16:08:30 medication in the cup. I put the top on there
16:08:33 initially backwards. The actual time to nebulize
16:08:37 takes, what, 10, 15 minutes? The nebulizer goes
16:08:41 until it starts sputtering and then once finished
16:08:45 with the treatment. That does not mean that all
16:08:48 of that drug has been nebulized. There is
16:08:51 residual volume or dead volume in nebulizers,
16:08:54 which generally ranges about one milliliter.
16:08:57 Considering that a unit dose of Albuterol is 2.5
16:09:01 milliliters, that's almost half of unit dose that
16:09:03 remains behind in the nebulizer.
16:09:06
16:09:06 There's certainly other forms of waste with
16:09:08 nebulizers. This runs continuously for the 10 or
16:09:11 15 minutes. The child is not breathing in during
16:09:14 all of that time, so there's waste during
16:09:17 nebulization. Need to be near an electrical
16:09:21 outlet, when I've already mentioned. It's not
16:09:23 portable. So it's really many, many challenges
16:09:25 with nebulizer treatments.
So ideally, you have a happy toddler that's sitting on a parents' lap and you certainly do need to use a face mask. People have taken corrugated tubing, aimed it at the child's mouth, and have done the blow by method. That does not work very well. You really don't get appreciable drug into the lower airways.

So this child is nice and cooperative, but what happens when they do not cooperate? I've heard the argument, well, if a child is crying during a breathing treatment, they're taking in big breaths and it's going to enhance the breathing treatment even more. We've all seen children cry, but how much have we really considered what happens during crying? How much time do they spend in inspiration versus expiration? Well, we'll take a look at a crying child. And we actually have inspiration/expiration labeled for you.

So that was a 20-second video clip, and of that 20 seconds I would guess that, what, maybe four or five seconds at the most was an inspiration? Most of the time was spent in expiration.

A study was performed to look at can you deliver
medications to the lower airway or I should actually say how does it compare to delivering medications to the lower airway in a child that's distressed, in other words, crying versus not crying, not distressed? This was looking at chromalin, which is an asthma medication back from the seventies and eighties which we really don't use anymore, because it's not a very good medication for asthma. P

Chromalin is absorbed across the respiratory epithelium and it undergoes hepatic and renal metabolism. They looked at the amount of chromalin in urine in 15 infants that were either distressed or not distressed. The not distressed infants excreted 0.43% of chromalin in their urine versus zero.01% in the distressed infants. And they are actually surprised with this finding.

They stated in the last sentence before their methods section, "We expected that with larger title volumes, we would have better delivery of drug in crying infants, but the opposite was true."

It makes sense when we think that have video clip that we just looked at. Children, when they're crying, they're not spending very much time in
16:12:15 inspiration. So I think the take-home message is
16:12:19 if you're doing a breathing treatment, and it
16:12:21 actually probably applies to metered dose
16:12:24 inhalers, the child really should be calm. And if
16:12:26 they're not calm, then we may need to wait and try
16:12:29 again later, although some children are headstrong
16:12:32 and they're not going to like it 28 days later
16:12:36 than when you first started the treatments on
16:12:38 them. I had a patient like that in clinic
16:12:40 recently who needed to be on nebulized tobramycin
16:12:45 for pseudomonas for the first time and CF.
16:12:47
16:12:48 And that brings me to one of the exceptions as far
16:12:50 as what -- can you deliver nebulized versus
16:12:52 metered dose inhalers. For some things, there's
16:12:54 no choices. Racemic epinephrine for croup. We
16:12:58 only have nebulized, although I was thinking about
16:13:02 this recently. And this is kind of heresy.
16:13:05 Primatene Mist is epinephrine. I wonder if one
16:13:09 can use that, but it's going to be a moot point
16:13:11 here because of the Montreal Protocol, which we'll
16:13:14 talk about here in a moment.
16:13:15
16:13:16 For CF patients, hypertonic saline, dianase toby,
16:13:20 which is tobramycin solution for inhalation, you
16:13:24 don't have any other choice than nebulized
16:13:26 treatments.
There are other ways to give nebulized treatments, and these are really, really nifty technologies that I'm not sure where we go with these. This is vibrating mesh technology. These devices have computer chips in them that sense the mesh and the solution to be nebulized. These meshes vibrate at a very, very high frequency, at the resonant frequency of the liquid and give you very, very fast, very efficient nebulization. These products produce more mono-dispersed particles. The Jet Nebulizer, as I mentioned, 0.1 to 30 microns, this is a very, very lower range, and in fact, these particles are only nebulized once. They don't have the larger particles that rain out and have to be re-nebulized over and over again.

These are very, very nice products. Unlike this compressor here, which was somewhat noisy, these are silent in operation. They're portable. They're battery operated. They can fit in the palm of your hand. The problem is, obviously, with the eFlow, it's quite expensive, and we don't have really any drugs with an FDA indication for these products. We almost had an indication for the eFlow in September of this year. Gilead is a pharmacy that developed Aztreonam for inhalation,
16:14:51 and their phase three studies were with the eFlow.
16:14:55
16:14:55 In September of this year, we expected the FDA to
16:14:57 approve Aztreonam for inhalation. The phase three
16:15:02 studies showed that it was safe. It was
16:15:04 effective. And very surprisingly, the FDA denied
16:15:07 the application. I don't know why. It's really
16:15:10 never been made public. The FDA has said that
16:15:14 they want more studies. And we're still in limbo
16:15:16 as to whether we're going to have Aztreonam
16:15:20 ventilation. If it had come out, the package
16:15:22 label would have said "Deliver with the eFlow
16:15:25 nebulizer."
16:15:26
16:15:26 Right now there's only one tobramycin solution for
16:15:30 inhalation and that's Toby delivered with an LC
16:15:33 jet nebulizer. There is another company that's
16:15:36 developing a tobramycin solution for ventilation
16:15:40 using the eFlow, but they're in very early
16:15:42 development.
16:15:43
16:15:43 As you can see, these other two products are
16:15:45 cheaper, but I don't know that there's really any
16:15:47 FDA indications of using these products with any
16:15:50 medications. There's a journal called Respiratory
16:15:51 Care, and in the December 1st issue this month,
16:15:55 there was a study in there looking at Dianase
delivered about the Omron compared to Dianase delivered with a Peri-LC jet nebulizer. It was equivalent, in fact, better with the Omron. It was more efficient. The respirable particles were delivered in a much better range than the Peri-LC Jet Nebuliser. This is one of those laboratory studies and it's there. Perhaps using this for Dianase would be useful, but I don't foresee that the package label is going to change from this small in vitro study.

These products are very, very nice. They make the treatments go much, much more quickly. If we had with Aztreonam for inhalation approved by the FDA, the treatment would have been perhaps three to five minutes versus the ten to 12 to 15 minutes with a conventional jet nebulizer and a compressor.

So we go on to metered dose inhalers. In 1955, there was a 13-year-old with asthma. And she complained to her father that there should be a better way to get asthma medications, somewhat analogous to her mother's hair spray.

Her father was the former chair of the Department of Pharmacology at Boston University, and he was
the president of a company called Riker Laboratories. He put together a team to develop metered dose inhalers, and within one year they had a new drug application with the FDA. So that was 1956. We just celebrated recently the 50th anniversary of the metered dose inhaler.

These devices have a propellant in the canister with the drug. There needs to be surfactant in this solution, also, so that it keeps the drug and the propellant homogeneous.

If you zoom in on the guts of this device, you have a metering chamber here. The size of that determines the amount of drug that is delivered. There's a metering valve with a hole in it that when the canister is depressed, that delivery valve with the hole goes into the metering chamber that forces the air out of the actuator nozzle, and this comes out at a very, very high velocity. You've got a plume of medication that comes out the inhaler, and there's something called the flashing process where the particles rapidly become smaller. Particles initially, when they come out, are 35 microns in size. And the initial speed of the particles coming out of the inhaler is in the range of 15 to 30 meters per second.
16:18:41 That's about one-tenth of the speed of a bullet coming out of a gun. Within 0.1 seconds, that speed decreases by half. These particles come out in a rapid string. They become smaller over time and then this is delivered to the airways.

16:18:59

16:19:01 So the problem, as I just mentioned, and the particles coming out in a rapid stream, there is multiple issues with putting the inhaler directly in your mouth. You have to coordinate pressing down and breathing at the same time. You don't have that much distance between the mouthpiece and the posterior pharynx and most of the particles will just impact against the posterior pharynx.

16:19:23 And particularly if you inhale quickly, you may not give the particles time for them to get smaller in size, which does happen with time. So there's really a ballistic quality of metered dose inhalers.

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16:19:38 To combat that, valved holding chambers were developed. There are different brands. This one is the Opti-Chamber. These are the Aero Chambers. This allows having the particles slow down in the holding chamber.

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16:19:56 Some studies have been done taking radioactive
labeled aerosols in these metered dose inhalers,
comparing, giving the inhaler, just directly placing it in your mouth, compared to using the holding chamber. There is a 10- to 17-fold decrease in radioactivity in the posterior pharynx when you use valved holding chambers.

There certainly are issues of using valved holding chambers, somewhat similar to issues with the nebulizer treatments. These are somewhat bulky. They're big and teenagers may not want to carry these around.

There's also somewhat of a more practical issue, which we normally don't think of. When you take these plastic inhalers right out of the box, there's a static electric charge on the walls of these inhalers, and you can have patients you start on a medication, they call you a week later and say, I'm not any better. That static electric charge can attract the medication to be on the walls of the inhaler. You can easily avoid that by, when you first take these devices right out of their box, you wash it with a dishwasher solution and that gets rid of the static electric charge for at least 30 days.
Alternatively, there's this vortex device. This is a metal inhaler that does not have the static electric charge. This is likely more expensive than these. I have no practical experiences with this vortex inhaler.

So we'll take a quick diversion here and talk about atmospheric science, because this is important with metered dose inhalers. Ozone is both friend and foe. We've heard of ozone alert action days in the summertime when there's no wind. Ozone is irritating to our airways when it is here at ground level, but up in the stratosphere, ozone is very important for the health of us and all living creatures on earth. It's earth's natural sunscreen.

The World Health Organization estimates that if the ozone layer decreased by 10%, annually there would be an increase of 300,000 non-melanoma cancers and 4500 melanoma cancers per year in the world. If you had just a 1% decrease in the ozone layer, then you'd have an increase of cataracts of 0.5%. So the ozone layer filters out the UVB radiation from the sun.

Back in the 1970's, some scientists discovered the
catalytic reaction, which they received a Nobel Prize for in chemistry in 1995. And everyone knows where I’m going with this. This has to do with chlorofluorocarbons, which was the propellant in metered dose inhalers until fairly recently. The way the catalytic reaction works is that sunlight reacts with the chlorofluorocarbon molecule to knock off a chlorine atom. That interacts with ozone, which is 03. That yields an oxygen molecule and chlorine monoxide. That, then, interacts with an oxygen atom to yield another oxygen molecule and freeze up that chlorine to once again destroy another ozone molecule.

One chlorine atom can destroy 150,000 ozone molecules. And bromine is 45 times as potent as chlorine. So this certainly could be a real issue, and in fact, studies have been done looking at what’s called the ozone hole over the Antarctic. These are depictions of this ozone hole. It’s measured in something called Dobson units. Less than 220, which is the more blue and purple area, defines the ozone hole. This is in September of 1980 and here’s September of 2008. This is due to our activity here on earth with
chlorofluorocarbons. Now, granted, certainly metered dose inhalers can be a small fraction of this, but as a result of this really startling occurrence that we brought on ourselves, in 1987 the Montreal Protocol was developed. That was a protocol in which, initially, the U.S. and 29 countries signed on. Since 1987 there have been a number of other countries that have signed on. Now I believe it's 191 countries have signed onto this in which the production of ozone-depleting substances is to be phased out in all of these countries that have signed on with the Montreal Protocol. And in fact, the original protocol stated that the ozone depleting substances needed to be decreased by half by 1998.

In another 13 days, we have a very significant date here in the U.S., because December 31st, 2008, is the last date that we can have CFC's as propellants in metered dose inhalers. The changeover has already occurred and there's a color handout back there that looks at the different Albuterol preparations and then Xopenex or leave Albuterol, which you can see they have to be primed in how often you wash the actuator plastic part of it.
There is actually one change of this which just occurred within the last week. The first medication ProAir HFA, it now has an FDA indication down to 4 years of age. So you can cross out the 12 and older and make that age 4.

So here's another off label reference in my talk. That patient I talked about at the very beginning, I switched them off of Pulmicort and put them on Flovent and Albuterol. Those medicines are medications are not approved by the FDA for patients less than age 4. Certainly we and people all around the country use these medications in infants and toddlers.

Getting back to the Montreal Protocol, the former Secretary General of the United Nations, Kofi Annan, said that this was the best example of international cooperation ever.

So there are differences between the chlorofluorocarbons and the HFA. The plume is different for the HFA. It's a softer plume. You also don't get the cold freon effect with the HFA inhalers. HFA stands for hydrofluoroalkane. So those now the propellants in metered dose inhalers.
And lastly, we have dry powder medications. It is possible in the manufacturing process to make dry powder preparations that are less than 5 microns in size, but those have very strange aerodynamic properties and really don't go into the airway well. So what drug manufacturers had to do was to create an excipient that the particles were latched onto, and that's generally lactose. In these preparations, one needs a high inspiratory flowrate. That creates turbulence, which separates the excipient from the actual drug particle. The excipient or the lactose rams against the posterior pharynx, whereas the particles go down into the airways.

Now, before using this inhaler, because this is a dry powder, these particles need to be protected from the environment, because humidity can render them useless. This shows the innards of the discus. There are certainly other inhalers that are more linear stubby devices that either have medications in line or one needs to load a gelatin capsule, and that is pierced. With the discus, there is a strip of medications. When one advances the thumb wheel, that medication is pierced and it's brought in line with the
As I mentioned earlier, you need a deep, fast inspiration to separate the excipient from the drug. So the dry powder inhalers, they certainly can be useful. They're not as bulky as carrying around an inhaler with a valved chamber, but you can't have infants and toddlers use these. You have to have a child that's older, that can cooperate with a deep, fast inspiration. So I would say generally above age 6, 7, or 8 at the minimum to use a dry powder inhaler.

So let's get on to the meat of this. We've talked about different modalities of giving medications. What about comparing these head to head? This is one of the more pivotal studies. It is a meta-analysis of studies. They did a MEDLINE search and there were three requirements to be included in this meta-analysis. Children had to be less than age 5. They had to have been seen in the emergency department. And they had to have received -- it had to be a randomized controlled trial in which patients either received beta agonist by metered dose inhaler with a valved holding chamber or by nebulizer.
And after they sifted through hundreds of studies, there were six that fit these criteria. They looked at what was better. The primary outcome was discharge from the emergency department. The line in the middle with one is neutral. If you're to the left of that, it favors metered dose inhaler with valved holding chamber. If you're to the right of that, it favors nebulizer. They found when they did this meta-analysis that metered dose inhalers with valved holding chambers was superior. It decreased admissions from the emergency department by 50%. They also looked at secondary indicators, such as clinical scores. That was improved, also.

This is another large meta-analysis in which randomized control trials were looked at, and they divided this into different categories. Delivery of short acting beta agonists in the emergency department, nebulizers, and metered dose inhalers with spacers are equally effective. Delivery of short acting beta agonists in the hospital setting. No difference in pulmonary function response between nebulizers and MDI with spacers. And the outpatient setting, no difference between MDI and dry powder inhalers. They said the use of nebulizers has not been adequately studied in
randomized control trials. And lastly, with inhaled corticosteroids, no difference between metered dose inhalers and dry powder inhalers, but there aren't any pediatric studies.

It's certainly easy to study acute asthma in that you have a sick patient. You can listen to wheezing. You can develop clinical scores. If they're old enough you can do pulmonary functions. A little bit more challenging with well-controlled asthma on a chronic basis. How do you separate out one modality versus another?

And then lastly, a Cochran Database Systematic Review looked at the various studies that included 2,066 children, 614 adults, and 25 trials. They found that the method of delivery beta agonist did not affect the hospital admission rate. In children, length of stay in the ED was significantly shorter for MDI with spacer. And their bottom line was metered dose inhalers with spacers produced outcomes that were at least equivalent to nebulizer delivery. Spacers may have some advantages compared to nebulizers in children with acute asthma.

Now, I realize this issue is very, very
polarizing. There are certainly medical personnel that swear by nebulizers are superior to any other modality of therapy. I would contend that the evidence actually is contrary that they’re equivalent. There are certainly many advantages to metered dose inhalers and that it’s much, much faster. And I really like this quote from a respected pediatric pulmonologist in Houston. I took this off of the pediatric e-mail listserv probably at least three or four years ago. "For a variety of reasons, including economic cost, routine beta agonist administration at Texas Children’s Hospital was changed from nebulization to MDI about three years ago in the OR, in the ICU, in the emergency department, and on the floors. It has been almost universally accepted. We still have many senior clinicians in the community who, via the old dogma, advise nebulizer therapy based on the theory of more deposition due to less need for cooperation in young ones. For my personal practice, the greatest evidence for the superiority of MDI has been the testimony of the vast majority of mothers of infants and toddlers. They almost all tell me the same story. It is quite difficult to impossible to get such children to sit still and wear a mask for 10 to 20 minutes. However, all mothers can hold their
child and get their cooperation for two to four puffs via valved holding chamber. Overall, it takes less time, but when I explain the bare minimum about aerosol deposition, these mothers convince themselves and me that their children get more beta agonist or inhaled corticosteroid deposited in their airways. It takes less time and both children and mothers are happier."

A second very helpful development is that we are no longer demonstrating an alternate model when sick asthma patients come into the ER and receive nebulized treatment while we are trying to teach them in clinic to use an MDI. So perhaps one might say this is a zealot and I'm a little bit of a zealot, too, but to try to get the pulse of the pediatric pulmonology community, I placed a survey on this pediatric pulmonology Listserv earlier this week. I had 182 responses to five questions. This is one of the five questions.

"For outpatient therapy of asthma, what is your preferred mode of medication delivery?" Two, the 182 said nebulizer. You've got about 28% MDI with valved holding chamber. About 5% with dry powder inhaler. And then this was an either/or MDI or dry powder inhaler.
I put another question on the survey, which I don't have a slide for. I asked this group, "For your institution, do you have a policy encouraging MDI valved holding chambers?" The responses could be yes, no, or no, but we'd like to move in that direction. And it broke out 30%, about one-third, one-third, one-third. One-third yes, have a policy. One-third don't. And one-third would like to move in that direction.

Similar to Dr. Mallory in Seattle, there was a place on the survey for extra comments. I received a comment yesterday from Seattle Children's Hospital. They have also converted to MDI's with spacers in their hospital. They look at their quality indicators of length of admission. They're just as good as when they were using nebulizers.

There's a statement in the Cochran systematic review of the nebulizer culture, and I really like that phrase. In my imagination, I see petri dishes in the microlab with little nebulizers growing on them. But putting that out of my mind, how do you change the nebulizer culture? This is a really interesting study that was done in
Australia in which they looked at the available evidence. They convened a group of caretakers in the ER: Physicians, nurses, respiratory therapists. They looked at best practices and developed a guideline for using MDI's with valved holding chambers. Their guideline was anybody less than critical asthma, they needed to go to the ICU, got an MDI with a valved holding chamber. I'm really not even sure about that rationale, but be that as it may, they had an intense education period over three months in which they taught everyone in all the shifts about this guideline. They wanted to teach the public about this, so they placed ads on television and the newspaper. They developed education guidelines. Four families explained the rationale for changing from nebulizers to metered dose inhalers with spacers. How to use MDI's with spacers. How to clean them. And then they implemented this. They've prospectively evaluated 200 perspective patients. The guideline was followed appropriately for 95.5% of the chain, so it can go done.

There was an excellent, excellent commentary that accompanied this article. I wanted to read a few paragraphs from this commentary. "In the second century AD, Ptolemy, the Greek astronomer and
mathematician, postulated that the sun rotated around the earth. His theory remained unquestioned for 1200 years. In the year of his death, Copernicus published his Copernicus system, showing clearly that Ptolemy was wrong and that, in fact, the earth and other planets orbited the sun. Galileo agreed with Copernicus, but was forced by the Inquisition to recant his support of the Copernicus system almost a century after it had been scientifically proven.

"The benefits of spacer devices over nebulizers in childhood asthma may not be as earth shattering as whether the sun or the earth is the center of the solar system, but it addresses an important issue in one of the commonest childhood disorders of our time. How many of us can honestly say that spacer devices have mainly taken the place of nebulizers in our emergency rooms and in our pediatric wards? For this reason, I think the paper of my pal and his colleagues is immensely important. It shows in an exemplary way what managerial steps need to be taken to adopt scientifically proven research results. For true consensus to occur, much explanation and discussion is needed. Didactic decisions will inevitably result in failure, because colleagues and their views, have not been
16:38:08 treated with respect.”

16:38:08

16:38:09 So I really like that commentary. It’s not going
16:38:12 to work if Mike Rock says we need the change in
16:38:16 AFCH to all MDI's with valved holding chambers.
16:38:20 It really needs to be a collaboration. I don’t
16:38:22 know if we're there. I don't know if we're ready
16:38:24 to go there or not. I think the evidence in this
16:38:26 talk says that we should. In the meantime, for
16:38:29 the general pediatricians in the office, you could
16:38:31 consider doing this in your office. For the
16:38:34 residents here, if your continuity clinic director
16:38:38 is not here, you could have discussions when you
16:38:39 see a child with asthma. Well, how about putting
16:38:42 them on an MDI with a valved holding chamber? I
16:38:44 think it's a win/win situation and we all want to
16:38:48 be winners in the end.
16:38:51
16:38:52 [Applause.]
16:39:01

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