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Special Topics : Chronic Obstructive Pulmonary Disease (COPD) : Bartolome Celli Interview - Special Topic of Chronic Obstructive Pulmonary Disease (COPD)

AUTHOR COMMENTARIES - From Special Topics

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Bartolome Celli

From the Special Topic of **Chronic Obstructive Pulmonary Disease (COPD)**

*According to our Special Topics analysis of COPD research over the past decade, the work of Dr. Bartolome Celli ranks at #5 by papers and #6 by cites, based on 83 papers cited a total of 3,255 times. Seven of these papers are included in the top 20 papers lists for the topic. In **Essential Science IndicatorsSM** from **Thomson Reuters**, his record can be found in the field of **Clinical Medicine**.*

Dr. Celli is on the faculty of the Pulmonary and Critical Care Medicine Division of Brigham and Women's Hospital in Boston, Massachusetts.

In the interview below, he talks with ScienceWatch.com correspondent Gary Taubes about his highly cited COPD research.

SW: Your most-cited paper is the 2004 *European Respiratory Journal* paper, "Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper" (Celli BR, et al., 23[6]: 932-46, June 2004). How did that paper come about and why do you think it's been so influential?

I was chosen by the American Thoracic Society to represent and draft guidelines for COPD diagnosis and treatment. That's not a research paper, per se, like the BODE index paper that is number two on the list.

It is a guidelines paper and that's why it's so frequently cited. It's the work of a large group of individuals working together. I was the chair of the group and put it together along with Dr. William McNee from Scotland.

SW: Okay, so let's talk about the 2004 *New England Journal of Medicine* article on the BODE index (Celli BR, et al., "The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in

chronic obstructive pulmonary disease," 350[10]: 1005-12, 4 March 2004). Tell us about how that research evolved and what you were trying to accomplish.

When I started my career in the mid-1970s, there was a fatalistic attitude toward the disease. It was truly a nihilistic attitude. It was thought that very little could be done for patients with COPD (emphysema and chronic bronchitis); it was felt that COPD was self-inflicted, resulting from smoking and the only therapy was to stop smoking.

I felt this was not the case and that, like many illnesses and diseases, there were many things that could be done. So we embarked on different areas of research to see what could be done, as other people were also doing at the time.

Much of our research was based on the belief that if we can't change the disease itself, at least we can change some of the problems around the disease and give people a better outcome. That led us to place a lot of emphasis into the investigation of prognostic indicators of outcome.

"COPD is a preventable and treatable disease."

SW: That implies that the existing prognostic indicators were inadequate. Is that true?

Yes. The way therapies were being measured 20 years ago is by how well they would bronchodilate patients, how well they would improve lung function. And we began to realize that many other dimensions that impacted on outcome independent of how affected lung function may be.

We began a series of studies around 1990 exploring the value of measuring exercise capacity, shortness of breath, and other variables that could be used as surrogate markers of outcome. This all led us to the concept that maybe we could create an index that would be used clinically to predict outcome.

That is how we came to the paper that may be the most important paper we have published—the 2004 *New England Journal of Medicine* article on the BODE index—and it took 10 years to reach that goal.

SW: So what exactly is the BODE index and what does it tell you?

It integrates body-mass index (BMI, what the B stands for), degree of obstruction (the O), dyspnea (the D), which is shortness of breath, and then finally exercise capacity (the E).

That was a significant shift in the paradigm of this field, when we pushed the agenda stating that the final outcome of patients with COPD was not only related to how bad their lungs were but that the intensity of other extra-pulmonary domains also had an effect. It opened ways to perhaps intervene in those areas and improve outcome even if we don't change lung function.

SW: What is the relationship with BMI?

We don't know why it happens, but people who have low BMI, people who are very thin, do very poorly if they also have COPD. Being a little overweight protects you from death, which is very interesting and somewhat counterintuitive.

SW: And that research took 10 years?

We started that work in 1994 and it was published in 2004.

SW: Did you start with the goal of developing a prognostic index, or did that idea evolve with the research itself?

In the early 1990s, we already had some indications that there were other independent predictors of outcome in patients with COPD that were independent from the degree of airflow obstruction, but it was in 1994 that we thought we might be able to incorporate several of them into an index. I guess it took longer than 10 years, if you think about it like that.

In the early '90s we did some six-minute walking distance studies; by that time some other investigators had looked at BMI, and it began to brew in our heads that maybe we could put it all together. Not until 2003 did we have the data that confirmed it could be combined into one index. We then applied the index to a larger validating cohort that we had followed over those six years and confirmed the value of the index.

SW: Why does this kind of research take a decade?

Well, this was a prospective study looking at mortality as an outcome. Very few studies had looked at mortality and what predicted it—very few.

SW: How many subjects did you have in this study?

We had in the end something like 859 for that first paper. Now we're up to 1,600 patients.

SW: And now that the BODE index is published and other people have confirmed its value, how is it actually used in the clinic? If it is, that is.

Let me tell you where its use is accepted. It is accepted as a way of staging of patients for transplants.

People with a very high BODE index, higher than 7, are candidates for lung transplants. We hope we will extend the use of BODE to everyday clinical practice.

The way you implement it is you see the patient; you measure the degree of obstruction with spirometry, the BMI, their endurance, by seeing how far they can walk in six minutes, and degree of shortness of breath, using the Modified Medical Research Council Scale. That gives you a number from zero to ten, and with that number, you stratify risk. The higher the number, the worse the patient will do.

So the international lung transplant community uses it to stratify people at high risk as needing a transplant. The people with a high number are those who are likely to die if they don't get a lung transplant. They're most in need.

SW: Were there potential predictors that didn't pan out and didn't make it into the BODE?

Absolutely. This is the way it's done: you first derive the index on a cohort. In that cohort, we explored over 24 factors that were thought to predict outcome: albumin, hemoglobin, many different lung functions, etc. These 24 potential factors were accumulated as possibilities between 1990 and 1994. We put together an initial cohort of 207 patients in this phase. The instrumental person on that was Dr. Claudia Cote, the second author. She collected those 207 patients at a VA Hospital where the informatics were very good. Then we tested them prospectively on the rest of the cohort in Venezuela, Spain, and the US.

In the end, the ones that panned out were the four that made this very nice acronym—BODE. We were lucky to have an acronym that is practical and meaningful: it BODES well for you or BODES badly for you. Sometimes in this business you need a little luck. You put in the effort, but sometimes it helps to have the wind blow your way.

Why did you choose Venezuela and Spain for the research?

First of all because I'm Venezuelan and I trained two Venezuelan doctors and then I trained

"When I started my career in the mid-1970s, there was a fatalistic attitude toward the disease..."

several Spanish doctors who went back to Spain. We had access to their clinics, so it was natural that we could cooperate with ease.

How has your research evolved in the half a dozen years since that BODE paper was published?

After the BODE paper, we embarked on a series of studies attempting to see if BODE could also be a surrogate marker of ulterior disease outcome. Our thought was if you have a disease that lasts 30 years, and you have to wait 10 years just to see the outcome of an intervention, could something else take the place of that final outcome and be used as a surrogate marker?

We published a series of papers evaluating the effect of rehabilitation on the BODE index at six months, the effect of lung volume reduction therapy and pharmacotherapy. All of these studies showed that the BODE index could be a surrogate marker of death down the road. It could be very useful.

In two of those—surgery and rehabilitation—BODE at six months predicts outcomes two and five years later. We have preliminary data, which we've so far published only as an abstract, and pharmacotherapy also reflected in that.

What's next for your research?

Right now we're working on biomarkers of COPD, specifically the use of blood or tissue biomarkers that might predict a patient's final outcome. The idea is if we could just draw blood without having to make any other measurements, that could tell us who's at risk of developing a bad problem, and then we could begin treatment much earlier.

What would you rate as your most difficult or trying professional moment?

My most difficult was probably in the early 1990s, just following a career path in research with very little funding. And I was doing this when I was not very junior, but middle attending level. That is hard, very hard. It's like trying to write a novel only to have the editors keep rejecting it.

Clinical studies do not receive a lot of support from funding agencies. You have to work your tail off to make a living and be able to continue your research. That transition was very hard. But perseverance won in the end.

How would you define the ultimate goal of your research?

I would like to be able to say that over the course of my career I helped patients with COPD.

How much has the treatment of COPD improved over the years that you've been working on the disease?

Significantly. We've found that oxygen therapy prolongs life or prevents mortality. We've found that pharmacotherapy can change the rate of decline of lung function, that pulmonary rehabilitation improves dyspnea and exercise capacity; that it prevents exacerbations and improves the quality of life, and we've shown that lung volume reduction surgery for some patients improves all of those as well as longevity.

We've come a long way. And what once was a negative attitude toward therapy is now much more positive. People do feel this disease is treatable, and that's reflected by companies which are now making products for COPD therapy.

What were the greatest challenges in performing and presenting your work?

The greatest challenge is that the field is under-funded. Let me rephrase that to give it the right flavor: it's the least well-funded, biggest killer in the United States by any institute that funds research. Getting funding to conduct studies in COPD has been very hard and it continues to be so. It's gotten a little better, but it still remains the least-funded largest killer in the United States. It's the fourth largest killer not just in the United States, but also in the rest of the world.

Why do you think that is?

It's still this feeling that COPD is self-inflicted. It's due to cigarettes. It's also a disease of poorly educated, poor people. You don't see a lot of executives smoking now. It's not like a heart attack that anyone can get. It's not like stroke or cancer. Those things anyone can get. Getting emphysema from smoking is a blue-collar disease, and I think that's why it's so poorly funded.

If you performed your research again, or published your paper again, what, if anything, would you do differently and why?

I would have liked to have had more numbers—2,000 patients instead of 859. That would have given us a little more precision. I don't think it would have changed anything else. I think the index is pretty good and our results have been corroborated.

What would you like to convey to the general public about your work?

I'd like to say that COPD is a preventable and treatable disease. That's the message for the general public. For the researchers and the younger people in medicine, I'd like to say that having faith in one's potential is very useful. It's essential, actually.

Final question: Are you satisfied with your career, and what you've accomplished in the years that you've been working on COPD?

Absolutely, I have had a ball. I've made a living and I hope I've been able to help others. You can't beat that. In addition, together with my wife, we have built a nice family. We put four kids through college and have five grandchildren. I don't have a house on Cape Cod. I'm not a member of a club. I don't have horses or a boat, but I wouldn't have had time to use them if I had. I've had a very nice life. I like what I do. ■

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Bartolome Celli's current most-cited paper in *Essential Science Indicators*, with 763 cites:

Celli BR, *et al.*, "Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper," *Eur. Resp. J.* 23 (6): 932-46, June 2004. Source: *Essential Science Indicators* from Thomson Reuters.


Additional Information:

Read an interview with [Jørgen Vestbo](#)—coauthor of the paper above.

KEYWORDS: COPD, GUIDELINES, DIAGNOSIS, TREATMENT, BODE INDEX, PROGNOSTIC INDICATORS, LUNG

FUNCTION, SURROGATE MARKERS, EXERCISE CAPACITY, BODY MASS INDEX, DYSPNEA, DEGREE OF OBSTRUCTION, EXTRA-PULMONARY DOMAINS, PROSPECTIVE STUDY, MORTALITY, LUNG TRANSPLANT PATIENTS, COHORT, BIOMARKERS, FUNDING, OXYGEN THERAPY.

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