Host: Welcome to the Anesthesiology journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and an associate editor for Anesthesiology, and you are listening to an Anesthesiology podcast, designed for physicians and scientists interested in the research that appears in our journal.

Today, we are speaking with the author of a publication that appears in the May 2017 issue of the journal. With us is Dr. Candela Solé-Lleonart. Dr. Solé-Lleonart is the first author of an article titled, “Nebulization of Antiinfective Agents in Invasively Mechanically Ventilated Adults.”

Dr. Candela Solé-Lleonart: Hi. Thank you very much for the opportunity.

Dr. BobbieJean Sweitzer: So, this systematic review and meta-analysis is part of the doctoral thesis of Dr. Solé when she was actually at the university Autònoma de Barcelona, Spain, under the supervision of the senior author of this study, Dr. Jordi Rello. The study was endorsed by the European Society, Clinical Microbiology and Infectious Diseases and the Center of Biomedical Research in Respiratory Diseases. So, Dr. Solé, I do not believe this is actually a primary research study, where you actually administered the nebulizing antiinfective agents. Can you briefly tell us what kind of research you did perform for this publication?

Dr. Candela Solé-Lleonart: That’s correct, that was not a primary research study. So, we are aware that worldwide, the nebulized antibiotics are regularly used for the treatment of respiratory infections in critically ill patients undergoing mechanical ventilation, without truly having any evidence for it. So, the goal of our research project was to evaluate the already existing evidence on their use, basically by analyzing their efficacy and safety; and then, through the GRADE methodology, to create a set of recommendations to help the professionals at the bedside. So, in fact, this research was the core work to develop an official position paper from the European Society of Clinical Microbiology and Infection, with a set of recommendations regarding their use in intubations; and it was in fact just reported online in April 13th at the Clinical Microbiology and Infection.

Dr. BobbieJean Sweitzer: Wow. That sounds pretty impressive. I must confess that I had never actually heard of the use of nebulized antiinfective agents being used or even available for use. Can you tell us how common this is, and give us some background on this therapy?

Dr. Candela Solé-Lleonart: Yes. Usually antibiotics are administered oral or intravenously in the case of critically ill patients, so in fact nebulization of antibiotics is just a different way of administration. And it was in fact an old technique that, it was dismissed some decades ago. The idea behind it is that by administering the antibiotic directly into the lung, we should have more efficacy in the resolution of the infection, and also less systemic adverse events such as nephrotoxicity. So, this could be particularly helpful potentially for the treatment of infections by resistant organisms, using drugs like aminoglycosides, which involve a high risk of nephrotoxicity.

So, this, and also the fact that the devices to perform the nebulization have improved importantly over the last decades—this has (sounds like: given a) renewed interest in the technique. For example, nebulized tobramycin and aztreonam are approved by the FDA for use in cystic fibrosis or bronchiectasis.

And then, on the other hand, to answer to your question regarding their use, yes, we can say that is common. In countries we have seen increasing prevalence of MDR organisms, like China, or India, or Greece, or Turkey, they are very popular for the treatment of patients. In fact, we did a survey two years ago which we call the SANEME, trying to assess this issue, and then almost 200 ICUs worldwide responded to the survey. And we found out that, almost half of them, for them it was a current practice to do it, and – even if it was not the standardized practice; and almost eight out of ten professionals saying that they did not use them, it was basically due to the absence of evidence-based guidelines.

Dr. BobbieJean Sweitzer: Wow. I didn’t realize there was all that background. So, in this study you reported on both. I believe, ventilator-acquired pneumonia and ventilator-acquired tracheobronchitis. Can you help me understand the difference between these two disease processes?

Dr. Candela Solé-Lleonart: Sure. So, both ventilator-associated pneumonia and ventilator-associated tracheobronchitis are a respiratory tract infection which is acquired while the patient is undergoing mechanical ventilation support. So, in the case of tracheobronchitis, the infection would happen in the upper airway—so, basically affecting trachea and main bronchi. And pneumonia would happen in the lower respiratory tract—so, in the alveoli.

The main problem with both is the lack of a diagnosed gold standard, which is challenging as they are still not well-defined entities. So, in both cases, the patient should have local signs of infection, like purulent respiratory secretions; also, systemic signs of infection such as fever or elevation of inflammatory markers; and then positive cultures for respiratory secretions. And the difference would be basically that, in pneumonia, we would have to identify radiological signs of infection, like infiltrates in the chest x-ray, which would be completely absent in the case of a tracheobronchitis.

However, as we know through our experience, chest x-ray in MV patients in ICUs are always difficult to interpret. So, the diagnosis remains really, really challenging. Another difference with both is that tracheobronchitis in ventilated patients is rarely reported as a ventilator-associated event as defined by the CDC in contrast with pneumonia, because usually hypoxemia is restricted to the episodes of VAP.

Dr. BobbieJean Sweitzer: Did you look at these nebulized antiinfective agents as the sole treatment of infections, or were they an adjunct to intravenous antibiotics?

Dr. Candela Solé-Lleonart: Generally, usually, nebulized antibiotics are not used as a first-line antibiotic. Therefore, we should assume that usually a first line of intravenous standard antibiotics will be already in place.

And then, regarding the antibiotics that we would nebulize, such as colistin or aminoglycosides, we defined in the group two different strategies to be evaluated that clinically had sense for us. One of them was the substitution strategy, which would be the administration of both nebulized and intravenous colistin or aminoglycosides; and then the other strategy was the substitution strategy, which would be the administration of either nebulized or intravenous colistin or aminoglycosides. So, in fact, we evaluated both the efficacy and safety outcomes according to those strategies to better differentiate clinically.

Dr. BobbieJean Sweitzer: And what did you find? What was the conclusion of your paper?
Dr. Candela Solé-Lleonart: The main findings was the absence of a clear efficacy for the treatment of ventilator-associated pneumonia. There was no clear impact on outcomes like mechanical ventilation duration, ICU stay, mortality, or clinical resolution. Even though there was a trend to higher resolution in their use against ventilator-associated pneumonia caused by resistant pathogens, only if the antibiotic was administered both intravenously and through nebulization.

And then, regarding their safety, we found that less risk of nephrotoxicity existed if the antibiotic was only nebulized; but on the other hand, we found that there was an increased risk of respiratory complications, particularly in severely hypoxemic patients at baseline—so, patients that have a PaO2/FiO2 ratio less than 200—which would be probably the grouping which we would have them administered.

Dr. BobbieJean Sweitzer: So, were you surprised by what you found?

Dr. Candela Solé-Lleonart: We were maybe not that surprised but high-
ly concerned on this increased risk of respiratory complications in these severely hypoxemic patients, because that means that basically we're using worldwide a technique that is not completely standardized yet, that there is no demonstrated efficacy benefits, and then not clear indications for it, and it might cause severe respiratory complications which might have potentially lethal complications. So, this was a very important discuss-

Dr. BobbieJean Sweitzer: So, we're going to come back to that a little bit later, because I want to explore that. I think you noted in your paper that there actually had been a development of a new generation of nebulizers, and I think you mentioned at the beginning of this inter-
view that this was sort of an older therapy that has been around, that maybe there's been this renewed interest, and that perhaps this was driven by the fact that there are these new, you know, generation nebu-
izers; plus, we have these new organisms and more resistant organisms 
that are presenting worldwide. So, I think most anesthesiologists are pretty familiar with the standard nebulizer for asthma therapies. But can you help our listeners understand exactly what nebulization is and how nebulizers work?

Dr. BobbieJean Sweitzer: I know your paper looked at publications on nebulized antivirals and antifungals in addition to nebulized antibiotics, and I think perhaps you were answering before about the – some of the complications. I didn't know if that was directly from the antibacteri-
als or all of these agents. But could you speak to a little bit of that, as 
was there a difference among these agents, either in their efficacy or their complication rates?

Dr. Candela Solé-Lleonart: So, regarding the antiviral and antifungals, that's right, we evaluated existing evidence regarding the nebulization of 
them. But we can say basically that there is none.

And then, regarding your second question about different drugs that we can use for nebulization, the fact is that the sample size of the studies 
that we included was so small that we couldn't do a subanalysis group for studying the different drugs. So, that would be an unanswered question.

Dr. BobbieJean Sweitzer: Sure, for another study. Is there any reason to think that nebulized treatment would be more effective against certain organisms?

Dr. Candela Solé-Lleonart: Usually, nebulization would be against MDR 
patients. This is usually what we do in clinical practice. For the pathogens 
that are sensitive, we don't usually need to treat them with nebulization of antibiotics. And then the antibiotics that are more analyzed would be colistin and basically aminoglycosides. Then there are other drugs like cephalosporins that are starting to be analyzed for their use in clinical practice. But again, the evidence is very low, and then we cannot analyze yet as for subgroups of different drugs. So, basically, we have no evidence regarding the different drugs.

Dr. BobbieJean Sweitzer: So, I know you've already addressed this to some degree, and I know your study focused not only on the effective-
ness of these nebulized agents but also on the safety of this delivery ap-
proach. And you've already mentioned about how there was an increased risk of complications in hypoxic patients, I believe. Did you find other complications, or were there any reduction? For example, I would think that perhaps by targeting the lung itself where the infection is, could you prevent, for example, maybe renal complications from the systemic adm-
istration of antibiotics, or did you find that there was any lessening of some complications even though you obviously did find an increase in certain complications?

Dr. Candela Solé-Lleonart: Yes. So, we searched for systemic complica-
tions like, as you said, nephrotoxicity. Also, we tested for neurotoxicity. 
But in fact, the problem was that some of the included studies were not looking specifically for adverse events, so this might be underestimated.

Then again, basically, respiratory complications; some cardiac adverse events were reported as well, secondary to these respiratory complications. For example, there were some cardiac events due to obstruction of the expiratory filter of the ventilator. Then, that is right, there was reduction of nephrotoxicity in the case of the subgroup of patients that were recei-
ving nebulized antibiotics only in the case of resistant organisms, and only nebulized but not IV.

Dr. BobbieJean Sweitzer: So, I believe I understand that a systematic 
review and meta-analysis are very, very dependent on the quality of the studies you are looking at, and I think you've already alluded to, you know, you didn't have enough information on, like, antivirals or anti-
fungals, or some of these other kinds of reports of complications. So, 
can you tell us a little bit about just how one starts to, you know, rate the quality of the data, or how you start when you're going to be doing a systematic review and analysis, so that you can find the appropriate articles? And then, do you rate them for quality or completeness?

Dr. Candela Solé-Lleonart: Sure. When you do a systematic review and meta-analysis, that is right, the – its quality depends basically on the studies that you are including in there. So, basically, in this case, everything started with a group of experts creating a set of clinical ques-
tions that we thought important to be answered, and then predefined outcomes to answer those questions. So, we separated them in safety outcomes and efficacy outcomes to evaluate the global effect of nebulization. Then, with this set of questions, we created a systematic search of the literature—a systematic review of it. And then we evaluated the articles that could be included in our meta-analysis, basically by a set
of inclusion criteria. And then, when we decided the articles that could be included in our meta-analysis, we evaluated their quality, trying to find out the risk of a bias of them, and then we included them in the meta-analysis.

Dr. BobbieJean Sweitzer: Had you had experience doing this kind of work before?

Dr. Candela Solé-Lleonart: No [laughter].

Dr. BobbieJean Sweitzer: Well, congratulations on getting a published paper in Anesthesiology with your first attempt. What do you think is perhaps the biggest weakness of your study?

Dr. Candela Solé-Lleonart: For us, it was the fact that the included studies had a very small sample size. Because of that, it prevented us from doing subgroup analysis, for example according to the drug, as we were saying before, or according to the type of device, for example, for nebulization, which would also be really, really interesting.

Dr. BobbieJean Sweitzer: You know, I think sometimes when we are used to seeing articles published in our English-language journals, often they only look at other English-language publications. But I — as I recall, you looked at some articles from a — quite a variety of countries: France; Spain; Thailand; Greece; Italy. Did you limit your search to certain languages or did you try to find any article, anywhere?

Dr. Candela Solé-Lleonart: Yes. There was no limitation in the search regarding time of publication; regarding type of article; regarding language. We (sounds like: made) no limitations. Then it is true that we eliminated the types of articles like narrative reviews, which cannot be included in a meta-analysis. Unfortunately, the other languages that we had some articles in, they were not includable in the meta-analysis.

Dr. BobbieJean Sweitzer: In your opinion, what do you think are the next steps to help us better understand if there is a role for inhaled anti-infective agents?

Dr. Candela Solé-Lleonart: So, we still do believe that there is a potential role for nebulized antibiotics in the treatment of MDR organisms, and then other innovative strategies, and this should be enforced by both regulatory agencies, like CDC, FDA, research networks like ours, CIBERES, or, like, societies — scientific societies such as ESCMID. But we are also convinced that further research — it really needs to be done to assess their efficacy and to clarify their indications, and most of it to clarify the adverse events, before we can recommend their use in clinical practice at the bedside in a safe way. So, for us, the main priority would be to develop well-designed randomized trials with predefined outcomes, and then standardizing the technique, particularly how to nebulize, which is key to avoid potentially severe complications. So, yes, we still need to do a lot of work on it.

Dr. BobbieJean Sweitzer: Yes. It takes a lot of time and money. Do you think it’s realistic that we — you’re going to be able to get more and better data?

Dr. Candela Solé-Lleonart: I think that with the development of new devices, this should be improved in the following years. I think that in clinical society we are really concerned about that. Resistance is a really important problem, and it’s going to be even worse in the following years, so we should try to find new solutions about it. Probably, nebulized antibiotics is just one of them, but I think that it’s really worth it to go on in this path, to find out if we can go on giving them or not.

Dr. BobbieJean Sweitzer: Yes, definitely. So, I understand — and you mentioned this, I think, briefly, at the beginning, that this systematic review and meta-analysis actually served to drive a position paper from the European Society, Clinical Microbiology and Infectious Diseases, and that this is reported online, I think in fact on April 13th of this year; in, I believe, Clinical Microbiology and Infection—is that the journal?

Dr. Candela Solé-Lleonart: Yes. That’s correct.

Dr. BobbieJean Sweitzer: That sounds like a really big deal, that your paper then actually was the basis for this position paper. Can you elaborate more on what that means; what position they took; what they’re advocating?

Dr. Candela Solé-Lleonart: So, for us, basically, it’s really important because we were really concerned after the SANEME survey about the extended use of nebulized antibiotics, worldwide in fact. So, after we did the meta-analysis, which is published in Anesthesiology, we were really, really concerned that the indication of them is not that clear at this moment; and then the — again, the severity of the complications is kind of concerning.

So, for us, the publication just after that of the set of recommendations of this position paper in an important magazine also, the Clinical Microbiology and Infection, here and in Europe, of the — our society of the — ESCMID, it means a lot of diffusion, so clinicians at the bedside might know that this is not the standard therapy. They already know that; but that it can imply complications that we are concerned about. So, before giving them, we should really wait for having a standardized way of delivering them, and then clear indications on their use; also, clear doses of the administered drugs, and a clear way of administering them.

Dr. BobbieJean Sweitzer: Well, congratulations. That’s wonderful, that your work is being put to such practical use and hopefully will improve the care of some patients. What do you find is a typical clinical situation that you think it really has an advantage in?

Dr. Candela Solé-Lleonart: So, I’m working (sounds like: after a very little timing) here. It is not really a (sounds like: particle-ized) administration. We are working on a protocol on them. In fact, the last time we administered them it was in a truly severely hypoxemic patient under a very, very limited situation. And then we had also respiratory complications, because, again, the patient was severely hypoxemic, and this increased his hypoxemia, so it did not work that well [laughter].

Dr. BobbieJean Sweitzer: How did it all turn out ultimately? Did the patient improve?

Dr. Candela Solé-Lleonart: Yes, with time [laughter].

Dr. BobbieJean Sweitzer: Oh, good. So, I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Dr. Solé-Lleonart, for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

Dr. Candela Solé-Lleonart: Thank you so much, Dr. Sweitzer.