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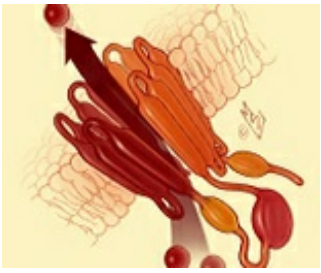

VOLUME 6 - ISSUE 4

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Pulmonary Exacerbations and the Microbiology of the CF Lung

Our guest author is John J. LiPuma from the University of Michigan in Ann Arbor, Michigan.

After participating in this activity, the participant will demonstrate the ability to:

- Describe how the complexity of the cystic fibrosis airway microbiome affects the management of pulmonary exacerbations.
- Summarize the limitations of in vitro antimicrobial susceptibility testing in guiding antibiotic therapy of CF exacerbations.
- Explain the role that bacterial species not routinely reported in cultures of CF respiratory specimens may play in contributing to pulmonary exacerbation and lung disease progression.

Unlabeled/Unapproved Uses

Dr. LiPuma has disclosed his discussion will not refer to off-label or unapproved uses of any drugs or products, with the exception of brief mentions of early-trial antibiotic combinations.

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Guest Faculty Disclosure

Dr. LiPuma reports that he has served as a consultant for Raptor Pharma, Aradigm Corp, and CURx Pharma.

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Podcast Transcript

BOB BUSKER: Welcome to this eCysticFibrosis Review Podcast.

I'm Bob Busker, Managing Editor of *e*CysticFibrosis Review. Our program today focuses on "Pulmonary Exacerbations and the Microbiology of the CF Lung," following up on our recent newsletter issue authored by today's guest: Dr. John J. LiPuma, Professor of Pediatrics at the University of Michigan in Ann Arbor.

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Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:
- **Describe how the complexity of the cystic fibrosis airway microbiome affects the management of pulmonary exacerbations.**
- **Summarize the limitations of in vitro antimicrobial susceptibility testing in guiding antibiotic therapy of CF exacerbations.**
- **Explain the role that bacterial species not routinely reported in cultures of CF respiratory specimens may play in contributing to pulmonary exacerbation and lung disease progression.**

Dr. LiPuma reports that he has served as a consultant for Raptor Pharma, Aradigm Corp, and CURx Pharma. His discussion today will not refer to off-label or unapproved uses of any drugs or products, with the exception of brief mentions of early-trial antibiotic combinations.

Dr. LiPuma, welcome to this *e*CysticFibrosis Review Podcast.

LIPUMA: Thank you very much for having me.

BUSKER: In your newsletter issue, you reviewed the recent research describing how diverse and how complex the airway environment is in patients with cystic fibrosis; how different the CF airway is from non-CF patients; and how challenging all this makes it to identify and treat the infectious organisms. I'd like to discuss how that information can translate into clinical practice — particularly in managing pulmonary exacerbations in people with cystic fibrosis.So please start us out with a patient scenario.

LIPUMA: The patient is an 18 year old young man with CF. He is homozygous for F508del and is pancreatic insufficient. He has moderate lung disease with an FEV_1 typically around 65 to 70 percent predicted. In the past his respiratory cultures have been positive for multidrug resistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus, Mycobacteria abscessus* and *Aspergillus*. Two years ago he received a prolonged course of multiple antibiotics targeting the mycobacteria. He's been in relatively good health for the past six months, receiving inhaled tobramycin BID on alternating months and azithromycin three days per week.

Two weeks ago he began to have increased cough, fatigue, and dyspnea. His sputum production has increased only

mildly, but he reports a couple of low grade fevers during this time. Oral ciprofloxacin and trimethoprim sulfa were prescribed five days ago, but his symptoms are unchanged. In clinic his FEV_1 is now found to be 50 percent predicted, and a chest x-ray is unchanged from images obtained on two occasions during the past year. Expectorated sputum is sent for culture.

BUSKER: Just to make sure we have a clear starting point, can we assume this patient is experiencing a pulmonary exacerbation?

LIPUMA: Yes, I think that by almost any definition you would say he is having signs and symptoms of an exacerbation.

BUSKER: Talk to us about what information you'd want to have to determine the most effective treatment for this patient.

LIPUMA: We would want to understand if he's adhered to the chronic antimicrobial therapy with inhaled tobramycin and oral azithromycin, as well as with his other routine CF care strategies including airway clearance, Dornase, hypertonic saline, etc. We'd also want to know if other family members are ill at this time, particularly with signs and symptoms of an upper respiratory infection. We may want to consider viral respiratory testing in him. We'd also want to know what his most recent sputum culture results showed, what antibiotics he was treated with when he last had an exacerbation, and how he responded at that time.

BUSKER: Let's say you do test for respiratory viruses, and that test comes back positive. How would that alter your management?

LIPUMA: His symptoms could be consistent with viral respiratory infection; in fact, in many ways it sounds like they are. So if a viral respiratory test is positive, this may make it less likely that antibacterial therapy will have an impact on his course. However, we really don't know how viral infection may affect bacteria that are likely also inhabiting his airways. Therefore, regardless of whether the test for a virus is positive, antibiotic therapy would still be warranted. The presence of virus might affect our prognostication about how he'll do with antimicrobial therapy, but the presence of virus doesn't necessarily preclude antibiotic therapy.

BUSKER: You said you wanted to know about his most recent sputum culture while you're waiting for the lab to report on his current one. How would knowing those results help?

LIPUMA: They would provide a starting point for considering antibiotic therapy. We'd want to know if a new bacterial species is recovered in the last sample; we'd like to know if mycobacteria or MRSA are present. We also want to emphasize that there is increasing evidence that CF airway infection typically involves a much more diverse group of bacteria than those we've conventionally associated with CF, and it's important to understand that not all of those bacterial species may be recovered in culture and/or reported as being recovered in culture by the clinical micro laboratory. The lab may refer to certain oral flora that would not be reported in cultures, things like certain streptococci and certain anaerobes.
So although previous culture results give us a starting point, they can't really reliably tell us what species may or may not be involved in causing this exacerbation.

BUSKER: Something else you said you wanted to know: how he was treated during his prior exacerbation and how he responded. How would that help you manage this exacerbation?

LIPUMA: Again, this is a starting point. If he had a good response to the previous therapy, we would consider starting with a similar treatment course. We're learning from studies of the CF airway microbiome that the community of bacteria inhabiting the lungs of people with CF is generally quite stable over time. There's not a great deal of fluctuation such that that completely different species replace others to result in a completely new community that may require treatment that is quite different from one exacerbation to the next.
Because these communities are rather stable, we think we might want to target them using the same sort of antibiotics we used previously.

BUSKER: Let's say that the lab report of the sputum culture you took comes back and Pseudomonas did not grow in that culture. Would you now stop targeting Pseudomonas?

LIPUMA: No, we really can't rely on culture to definitively rule out that Pseudomonas is not present. Eradication of Pseudomonas after years of chronic infection is really very unlikely. So even though this may not show up in culture now, it's unlikely that Pseudomonas is completely gone.

BUSKER: Let's say that the lab report that's just come back indicates that more than one bacterial species has grown in culture. Would knowing which species is present in the greatest density help guide therapy?

LIPUMA: Intuitively, this seems to make some sense, but in fact, there is really no good evidence that this is the case. For one thing, quantitative culture is quite unreliable; it depends on which species may be favored by the culture conditions being used. Another thing to keep in mind is that it's also possible that species that may be present at a relatively lower density could have a disproportionate impact on contributing to exacerbation. So looking at relative densities of different species is not particularly worthwhile.

BUSKER: Let's go back and say that Pseudomonas is recovered in this sputum culture. What about antibiotic susceptibility testing? How important would those results be in managing this patient's exacerbation?

LIPUMA: This is a difficult question in some ways. We've always relied on antibiotic susceptibility testing to guide therapy; however, data over the past decade has shown a fairly poor correlation between choosing antibiotics based on in vitro susceptibility testing and clinical outcomes of exacerbation. We are now learning that there are many possible reasons for this disconnect between antibiotic susceptibility testing and outcomes.

For one thing, we've already mentioned that there seem to be many more species involved in CF lung disease than we had previously appreciated. We also know that many of these species may not be recovered in culture or reported by the clinical microbiology laboratory. Susceptibility in the laboratory may differ from what actually goes on in the lung, because within-lung susceptibility may be affected by other species in close proximity within the lung. The growth rate of bacteria in lung may affect their susceptibility to antibiotics. So the way bacteria grow in lung may be quite different from the way they grow in the laboratory for susceptibility testing.

Finally, we now know that there could be mixed populations, particularly of a bacterium like Pseudomonas, that differ with respect to susceptibility. So the same strain of Pseudomonas coming from one part of the lung may have a very different susceptibility profile than Pseudomonas coming from another part of the lung.We are starting to understand why there is a poor correlation between susceptibility testing and clinical outcomes, so therapy of exacerbation is guided by culture results and susceptibility testing, but ultimately it's very empiric.

BUSKER: Thank you for that discussion. We'll return with Dr. John J. LiPuma from the University of Michigan in just a moment.

Hello. I'm Bob Busker, managing editor of *e*CysticFibrosis Review..*e*CysticFibrosis Review is a combination newsletter and podcast program delivered by email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to pulmonologists, gastroenterologists, infectious disease specialists, pediatricians, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists.

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BUSKER: Welcome back to this *e*CysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. We've been talking with Dr. John J. LiPuma from the University of Michigan about how a more complete understanding of the microbiology of the CF lung can aid in improving the treatment of pulmonary exacerbations. Let's continue with another patient scenario.

LIPUMA: A 12 year old girl with CF comes to clinic reporting increased cough and decreased appetite and energy during the past 10 days. In the past, throat swab cultures had been intermittently positive for *S. aureus* and *Haemophilus*. She was treated with an eradication protocol when her throat swab was first found to be positive for Pseudomonas at age 6. This was repeated when an induced sputum culture was again positive for Pseudomonas at age 8. She was found to be Pseudomonas-positive again at age 10. She began to expectorate sputum at age 11, and four consecutive sputum cultures, including one two months ago, had been positive for Pseudomonas. Her FEV_1 in clinic is 90 percent; typically, it has been around 100 percent. Her mother reports that she has been compliant with routine therapies at home, including airway clearance, Dornase, hypertonic saline, inhaled tobramycin, and azithromycin.

BUSKER: So again we have a patient with a pulmonary exacerbation. Tell us about your next steps in management.

LIPUMA: The next steps would be to initiate a more aggressive antimicrobial therapy course and choose agents you would expect to be active against Pseudomonas. But considering that other bacterial species may be contributing to the increase in symptoms, we would repeat the sputum culture.

BUSKER: I think a question a lot of clinicians might have right now is, why not hold off on starting any therapy until the susceptibility testing of the Pseudomonas is available?

LIPUMA: Susceptibility testing can be used as a starting point to guide therapy, but as we saw in the last case, there are many possible reasons why choosing antibiotics based solely on susceptibility testing has not been shown to predict outcomes.

BUSKER: So you send the lab a sputum sample, and the results come back reporting two different strains of Pseudomonas in culture. What does that mean and how does that affect your management?

LIPUMA: This comes up fairly frequently. The lab will report two strains of this or that species, in this case Pseudomonas. But in reality, this most likely represents different morphotypes of the same strain. These different morphotypes, we believe, reflect adaptation, or some people say evolution, of Pseudomonas during chronic infection, so it doesn't mean that a new strain is now causing infection or that different therapy is indicated. The different morphotypes may have different susceptibility profiles in vitro, but the important thing is to recognize is, the infection is not a new strain, which would be reason to alter the therapy that's been used in the past.

BUSKER: Let's look at that report from the micro lab again. Let's say, in addition to the Pseudomonas, a strep species, was also recovered in the culture. How would that change your management?

LIPUMA: Strep species are common inhabitants of the upper airway. We have recent evidence that they can be present in lower airway as well, and there is some evidence that certain strep species for example, *S. milleri*, can contribute to lung disease in CF.
In fact, in one report, treatment specifically targeting *S. milleri* was associated with a good clinical outcome. So we shouldn't necessarily ignore that species, as it may contribute to exacerbation symptoms.

BUSKER: What about other pathogens that may not have been recovered in the routine culture? Would you expect those could also be contributing to this patient's exacerbation?

LIPUMA: Yes. In fact, there is growing evidence that anaerobic species common in the oropharynx can be found in appreciable quantities in lower airways and may contribute to disease, as well.

BUSKER: That seems rather counterintuitive. The lung is such an oxygen-rich environment, how could anaerobic species survive?

LIPUMA: Recent studies have shown that CF sputum is actually largely anoxic. Further, severely damaged parts of lung may be relatively oxygen-deprived, so it's becoming increasingly clear that diseased lung and mucus provide a niche that favors anaerobes. Further, we should remember that all of the typical CF pathogens, including *Pseudomonas, Staphylococcus, Burkholderia, Stenotrophomonas,* and *Achromobacter,* are all capable of growth in very low oxygen.

It's important to recognize that as we continue to learn more and more about CF microbiology and considering things like anaerobes, for example, that treatment of exacerbation still is by and large empiric.

BUSKER: Dr. LiPuma, thank you for today's cases and discussion. Let me ask you to take a moment now to look to the future for us. What advances do you see happening in improving the management of CF infections?

LIPUMA: We're learning a great deal about the microbiology and ecology of airway infection in CF. It's hoped that this new knowledge will translate into new strategies for preventing or treating infections in CF, including CF exacerbations. At the same time, we'll be assessing the role, if any, of newer antibiotic agents, including combination drugs such as ceftolozane/tazobactam and ceftazidime/avibactam in the treatment of CF lung infection. And we shouldn't forget that a number of the other new strategies are coming out, for example with CFTR modulators, that will have impacts on infection in CF that we really can't anticipate at this time.
In general, I think it's fair to say that the future is fairly bright.

BUSKER: Thank you for sharing your thoughts, doctor. Let's wrap things up now by reviewing what we've talked about today in light of our learning objectives. To begin: how the complexity of the CF airway microbiome affects the management of exacerbations.

LIPUMA: Until fairly recently, we thought only a small handful of bacterial species contributed to lung infection, and therefore exacerbations, in CF. We're now learning that the microbiology and the ecology of infection in CF are much more complicated than we previously appreciated, and I think this means we have to take a fresh look at strategies to treat exacerbation.
We're learning an awful lot about microbiology in CF, and I think this has potential to change our approach to exacerbation.

BUSKER: And our second objective: the limitations of in vitro antimicrobial susceptibility testing in guiding antibiotic therapy for CF exacerbations.

LIPUMA: The more we learn about CF microbiology and the way bacteria may be living within the CF airways, the more we can understand why in vitro susceptibility testing and choosing antibiotics on that basis has not always correlated very well with clinical outcomes. The hope is that as we learn more, we can start to modify our approaches to therapy of exacerbation, but until that time therapy remains largely empiric.

BUSKER: Finally, the role that bacterial species not routinely reported in cultures of CF respiratory specimens can play in contributing to pulmonary exacerbation and lung disease progression.

LIPUMA: We're learning that species may be present in the CF airways that have not been routinely looked for in the clinical laboratory, or, if found in culture, have been ignored as upper airway contamination but we now think may have a role in causing disease in CF. Certain of these species may interact with some of the more typical CF pathogens to cause them to behave differently in the lung, and some of these species that haven't been reported by themselves may act as pathogens, for example, by having certain proinflammatory components and therefore contribute to inflammation within the lung.

BUSKER: Dr. John J. Lipuma from the University of Michigan, thank you for participating in this *e*Cystic Fibrosis Review podcast.

LIPUMA: Thank you, it's been a pleasure doing this. I really welcome the opportunity to participate in this program. I hope your listeners find it educational and worthwhile. Thank you very much.

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