Practical Considerations in the Management of Cystic Fibrosis: Frequently Asked Questions

1. Is newborn screening and diagnosis making a difference in cystic fibrosis (CF)?

**Stacy Vandenbranden, APN:** The CF registry shows steady improvement in median growth indices by 5-year birth cohorts,\(^1\) so I would say that we can clearly see there is an improvement with the implementation of newborn screening. The Centers for Disease Control and Prevention report\(^2\) on newborn screening for CF presented long-term benefits including from a nutritional perspective (ie, improved growth, reduced risk of a failure to thrive), pulmonary benefits (ie, improved radiographic and scwachman scores), and potentially reduced mortality.\(^2\)

**Craig Lapin, MD:** Because initiation of newborn screening requires significant proof before it becomes mandated, there had to be significant evidence that it was better than receiving a diagnosis later in life. Although it took a little bit longer, there have now been studies now that show that newborn screening is associated with pulmonary function improvement and, in fact, better survival as well.\(^3,4\)

**Ms. Vandenbranden:** At the North American Cystic Fibrosis Conference (NACFC) this year they presented information that showed newborn-screened patients are less likely to be malnourished, hospitalized, and acquire *Pseudomonas aeruginosa*.\(^1\) The benefit of newborn screening is extending through childhood.

**Dr. Lapin:** Those data are actually different from one of the earlier studies from Phil Farrell in 2003. It was a 1-center study that suggested that there might have been earlier acquisition of *Pseudomonas*, but I think infection control has become significantly better since that time. We are much more cognizant of the need for infection control in CF. In fact, most places often will have cohorting of screened newborns if not other patients.

2. Can you discuss the spectrum of disease associated with CF, and how genotype correlates with the different presentations we see in clinic?

**Dr. Lapin:** A relationship between genotype, pancreatic insufficiency, and liver disease was found by Peter Durie and colleagues\(^6,7\) almost a decade ago. The answer for pulmonary disease has been much more difficult. Currently, we do not believe that there is a direct correlation between a CF genotype and pulmonary phenotype. However, we have begun to see the results of the gene modifier studies bear out, and in doing so we have identified potentially 2 genes on chromosome 11 and 20,\(^8\) which is different from *CFTR*, which is located on chromosome 7, that are associated with pulmonary outcomes. So we are
beginning to get more answers as to what may affect the pulmonary phenotype in CF.

**Ms. Vandenbranden:** It is important to stress in this question that a patient's phenotype or how an individual person's symptoms appear is influenced not only by genes, but also by environment.

3. **How necessary is chest physiotherapy for pediatric patients who are not experiencing active symptoms?**

**Ms. Vandenbranden:** Dr. Stephen Stick is presenting compelling data this year at the NACFC that lung disease in CF begins very early in life, even in asymptomatic infants. Specifically, he showed that 20% of infants diagnosed by newborn screening will have bronchiectasis, mucous plugging, and air trapping by 1 year of age, and that worsens over time. In addition, 80% of children by age 6 will have evidence of bronchiectasis on chest CT. Airway clearance is what we have to really combat this disease progression.

**Dr. Lapin:** There are changes that occur in the CF lung even if a person is asymptotic (ie, no productive cough or clinical symptoms). There is a strong suggestion that having mucous adhere to the airway in 1 area will increase the inflammatory response. Thus, if we can do anything that helps to shift secretions or mucous from one area to another more proximally, especially if it is something that we can teach our families and patients to do, we should and in that way when patients do get sick, caregivers are able to go ahead and better deliver this type of care. There is no question that doing routine regular therapy in asymptomatic patients is something that is standard of care and should not be skipped on.

4. **Is inhaled tobramycin or inhaled aztreonam best in treating *P aeruginosa***?

**Ms. Vandenbranden:** Both of these agents have been shown to be effective in treating chronic *Pseudomonas* infection. There is one head-to-head study that looked at these in comparison looking at parameters like time to intravenous antipseudomal antibiotics, need for hospitalization, and a relative change in percent forced expiratory volume in 1 second (FEV₁) after 4 weeks of treatment. The head-to-head trial did appear to show a slight advantage to inhaled aztreonam in that its use was associated with a longer period until the next intravenous course of antipseudomal antibiotics, a slightly improved change in lung function (ie, FEV₁) after 4 weeks of therapy and fewer hospitalizations. However, that is one study, and I think that we will have to look and see as time goes forward how that pans out.

**Dr. Lapin:** There is no question that both therapies are effective inhaled antibiotics. Again, the data in that head-to-head study are something that we
need to have confirmed. There are potential confounding issues based on the fact that most, if not all, of the patients had received inhaled tobramycin before. Thus, being on chronic inhaled tobramycin might have changed a patient's "placebo response" compared with the group that received inhaled aztreonam. Still, they are both good inhaled antibiotics that are effective in this patient population.

**Ms. Vandenbranden:** In addition, it's also important to look at not only drug efficacy, but also what works best for the patient. As we know, inhaled aztreonam requires 3x a day delivery while inhaled tobramycin requires 2x a day delivery. It may be best to have a twicedaily-delivered drug vs one that is delivered thrice daily.

**Dr. Lapin:** The inhaled aztreonam is much faster to deliver using the eFlow® device (Pari Medical, Midlothian, VA), but in speaking with families the cleaning time of the eFlow® device basically takes the same amount of time. Thus, we really do need to look at what works best for the patient and family.

**Ms. Vandenbranden:** It is almost as important to note that only inhaled tobramycin has been demonstrated to be effective in eradication of first acquisition of *P aeruginosa*. Aztreonam is still being studied for this population.

5. **How do we motivate patients with CF when treatment regimens become tedious?**

**Dr. Lapin:** One of the things that we as clinicians need to do is focus on how CF-related therapies keep folks in optimal [health] status. We want them to be able to have a full life and be able to take advantage of new therapies that are currently being developed. Thus, we need to say to patients that "It may not seem like a significant effect right after you take this medicine; it is one of those therapies that will help you stay well, and because of that you will be able to do the things that you want to do as you get older." We also need to stress to our patients that because they are going to be much better they will not have as many changes to their lungs and health so that when new medications become available they can take full advantage.

**Ms. Vandenbranden:** I think all of our patients really desire normalcy. Because of that I try and help families think about their treatment regimens as not something that makes them abnormal, but something that allows them to live a normal lifestyle -- shifting their thinking about their regimen and as Dr. Lapin said, looking at their perception of benefit. It is hard to take a medicine every day that just keeps you at the same place, because of that we need to help patients understand what their therapies are doing when they take them.

6. **When will new medication that targets genetic defects in patients who are homozygous delta 508 in their CFTR be available?**
Dr. Lapin: Well, everybody is hoping sometime soon, and the Cystic Fibrosis Foundation itself is completely committed to discovering new therapies that will work in patients who are homozygote or heterozygote for the delta F508 mutation in their CFTR gene. The question of when or how is dependent upon a number of factors. For instance, will VX-809 in combination with ivacaftor provide clinical benefits, and if so, how much clinical improvement will it provide?\[^{15}\] In addition, there are other therapies being studied (ie, ataluren, VX-661), which may provide benefit.

Ms. VandenBranden: However, although these therapies are promising, they do not alter the gene, but instead improve the CFTR protein function caused by the gene defect. The current medication that is completing phase 3 trials is only beneficial for people with a specific mutation, G551D, and it is more of a functional cure.\[^{16}\] The therapy (ivacaftor) will have to be taken on an ongoing basis. It is worth noting that it is not known yet how much it [ivacaftor] will reduce other treatment requirements.

7. What is the role of chronic infection of methicillin-resistant Staphylococcus aureus (MRSA) in CF? What are the best preventative measures we can put in place from a home and school setting to assist in infection control and wellness?

Dr. Lapin: Well, for a fair period of time, people thought colonization by MRSA might not make that much of a difference in patients with CF. However, more recent studies that looked at registry-wide information, and therefore had better ability to determine the role of MRSA in CF, certainly show that MRSA is a problem.\[^{17,18}\] However, the important part here is colonization vs acute infection. When a patient starts to have chronic infection with MRSA is generally when we see a somewhat faster decline in pulmonary function and a slightly higher mortality risk.\[^{17,18}\] There is definitely an association with increased disease, and currently, there are studies that are ongoing to look at whether we can affect clinical outcomes through an eradication strategy and/or therapy. Eradication of MRSA is a lot more problematic than eradication of Pseudomonas.

Ms. VandenBranden: It will be interesting to see what those studies show as far as the best methods and the success in eradication of MRSA. I think how MRSA interacts with the CF airway, and what the best intervention is are tough questions. It's good to know that it is currently a top priority for research among the CF community.

As far as infection control we should refer back to the written consensus guidelines from the Cystic Fibrosis Foundation.\[^{19}\] All patients and families affected by CF should be educated about the risk of cohorting with other individuals with CF. In addition, I would encourage families, especially of young children, to avoid elective exposure to people who are sick, whether that is...
having a child in elective daycare, or a Gymboree class. Avoiding elective activities is especially important during the viral season and the winter months when children are small so that exposure to sick kids and people is minimized.

In school, we have had children who are in the same school as other children with CF, and in that case we have worked with schools rigorously to make sure they are in separate classrooms and are not in common activity classes such as gym and music together. We encourage families to be open about their child's diagnosis with their schools for this reason, because then if there is another child with CF, the proper accommodations can be made.

The bottom line is that we need to be educating about how organisms spread (ie, largely through contact transmission, teaching hand hygiene responsibility as well as emphasizing the personal space rule (ie, a 3-foot difference) to children with CF. Teaching both those items at a young very young age so that children are responsible for their own hand hygiene is important.

Dr. Lapin: This is completely right. The emphasis on handwashing with water or waterless soap is really one of the easiest and most effective ways to cut down on transmission. Having handwashing become a habit is one of those things that makes a huge difference in patient outcomes. I agree with Stacy that we should be using the infection control guidelines as a roadmap -- referring back when there is a question because it contains s a wealth of information on what to and how to work on things.

I think one of the aspects of school care is that it is very important to go ahead and try and avoid comingling. Still we do not want to ostracize a child. For, instance we recently had a family that maybe was carrying it [infection control] too far, pointing out the differences between the two kids, and it was almost a stigma or ostracizing the other child. We need to work with the school to make school and infection control as seamless and as effective as possible, while allowing them to enjoy school.

Ms. VandenBranden: Right. I think it is important with families to stress that even if you are aware of another person with CF in your environment, one has to consider everyone around you whether that is the person next to you on the airplane or the person in the grocery store. It's why going back to the basics of personal space and hand hygiene is really the most effective all the time at preventing infections.

8. How can we help patients achieve and maintain adequate weight?

Dr. Lapin: One of the first things is education as to why weight is important -- highlighting the association between weight, good health, and maintenance of pulmonary function. We also need to communicate with the patient (and his or her family) where the patient lies in terms of nutritional status. Is it good? Is it not
there yet? Is it actually pretty poor, and then to go ahead and give them targets to aim for. One of the most important things we can do is to go ahead and communicate where a person is and why it is important for them to try to stay in or move into good nutrition.

**Ms. VandenBranden:** Newborn screening provides us with an opportunity to establish a growth trajectory from the start, and it is a good place to start with the counseling of what our expectations of growth are in children with CF. Regardless of what age patients are, I counsel parents that our expectation is that children with CF grow normally and reach their genetic height potential. With that is the caveat that for some children, this goal is easier to reach than for others, and for some children, it will take more effort and more intervention, but that is still our expectation for them. Goal setting from the very beginning helps families realize the importance of nutrition.

**Dr. Lapin:** Setting up nutritional goals, and focusing on it as an expectation and a target also helps to set up or work on the idea that if things are not going well, if a patient is failing to thrive it is not anyone's fault. CF is a disease where it can be extremely difficult to meet those nutritional expectations even if a patient is doing all the right things. It's nobody's fault if a person is not growing well, but the expectation is that in spite of CF, we want a child to grow well and to be average and adequate because of how it can affect long-term health. Setting expectations therefore sets up further discussion for families if they are not growing well.

**Ms. VandenBranden:** For clinicians, it is important to have a good nutrition algorithm or a pathway in front of you, so that you do not miss something along the way as you address nutritional gaps, such as adequate enzyme dosing with what I call anticipatory increases over time. In other words, not waiting until a patient's growth has dropped off to increase enzymes, but to keep them at the same dose per weight over time. Taking such a measure allows patients a good growth trajectory. In addition, we need to be addressing common comorbidities that can impact appetite like reflux and constipation, or looking for CF related diabetes. Finally, we need to be sharing that algorithm with patients and their families to help them achieve nutritional goals.

**9. When do we start thinking about the nutritional support when they haven't been able to achieve their weight goals?**

**Dr. Lapin:** If a clinician is finding that a patient does not have good nutritional status and is failing and not achieving the goal, we need to start revisiting the conversation about expectations with the patient and family. With that algorithm, as you set up a criterion for enteral feeds, it is important to go ahead and start that conversation with the patient and family usually at least 6 months in advance. So we tell them "We are going to still work on nutrition, but here is the target; we are going to work just as hard as we have been doing this over the last
6 months. However, if we cannot reach this particular weight goal in spite of everybody doing the right thing, then the next step is to go ahead and to establish enteral feeds."

**Ms. VandenBranden:** We generally start to consider an enteral feeding option in the presence of a persistent calorie gap, and that is how we present it to families. "Your calorie needs exceed your ability to take in calories. We have this gap, and we have gotten rid of all the other things (eg, reflux, constipation, etc) we have looked at all the other potential contributors, and we still have this gap. A good solution to the calorie gap is to introduce enteral feedings so that we can make up that gap and you can reach your weight goals." This way, it is not anybody's fault; it's just a fact. "Your body needs more calories than you can take in, and here is an adequate solution for it".

10. How does a clinician help a patient with CF manage symptoms of depression either due to them experiencing a recurrent pulmonary exacerbation, or just due to their disease course overall?

**Dr. Lapin:** Yes, I think depression and anxiety are an area in CF care that we are starting to see as the priority due to the linkage between health and depression, and between adherence to therapy and depression. There is a study that I know actually hasn't been published yet, it's abbreviated by the word underway by the name of TIDES ([www.TIDES-CF.org](http://www.TIDES-CF.org)), that is suggesting that anxiety may actually play as much if not more of a role than depression does in CF care. I think that we need to increase our awareness of depression and anxiety in our patients with CF and increase referral to mental health professionals, to help or to bring them into the CF team. Hopefully, we are beginning to systematize that [diagnosis and manage depression and anxiety] as well.

**Ms. VandenBranden:** I think it is also helpful to encourage patients and families that yes, we do ask a lot of you in your daily therapy, and we are aggressive about treating complications, and the reason behind that is because we as clinicians anticipate that there will be therapies that will be beneficial to your care and outcomes in the future. Because of that we really need to work at maintaining your health so that you will benefit from those therapies when they become available.

**Dr. Lapin:** I think that one of the things that Stacy alludes to, too, is that we as clinicians need to acknowledge the difficulties that exist for patients with CF -- really acknowledge of the burden they are experiencing. We also should acknowledge how impressive our families and our patients are to go ahead and do all the things that we ask them to do, and still proceed through and have all the other issues of life that occur. Praising and recognizing what our families are doing is also an important part of their care.
References: