Dealing With End-Stage Pulmonary Arterial Hypertension

Guest editor and editor-in-chief-elect Hap Farber, MD, led an insightful—and lively—discussion among an international group of practitioners to share their opinions and expertise on the state of the art in managing end-stage pulmonary hypertension. The discussants are Drs. Olivier Sitbon, Professor of Respiratory Medicine at the South Paris University, France; Maria Crespo, associate medical director of the lung transplant program at the University of Pittsburgh; and Adaani Frost, professor at the Institute of Academic Medicine, and director of the Houston Methodist Lung Center.

Dr. Farber: Let’s start by introducing today’s group for this discussion. I’ll start with Olivier.

Dr. Olivier Sitbon: Hello, I am Olivier Sitbon. I am Professor of Respiratory Medicine at the South Paris University, by definition is south of Paris (laughter), and I am involved in the PH field since maybe 20 years, maybe more. I am interested in particular in treatment strategies in patients with PH.

Dr. Crespo: My name is Maria Crespo. I am the Associate Medical Director of the Lung Transplant Program at the University of Pittsburgh Medical Center. My field is lung transplantation. My biggest interests are patients who have interstitial lung disease and pulmonary hypertension related to collagen vascular disease and particularly, scleroderma patients.

Dr. Frost: I am Adaani Frost. My address isn’t as cool as Olivier’s (laughter). I am a Professor at the Institute of Academic Medicine and the Director of the Houston Methodist Lung Center in Houston, Texas, and my involvement with pulmonary hypertension has been for over 20 years. Prior to that, I ran the lung transplant program.

Dr. Farber: Today, we are going to discuss end-stage pulmonary arterial hypertension (PAH). First, we should define the entity so that we can better discuss it. Adaani, how would you actually define end-stage PAH? When do you consider a patient to have end-stage PAH?

Dr. Frost: Well, that’s sort of defined by 2 things. Number 1, that you’re at the end of your therapeutic alternatives from a medical point of view; and number 2, that the hemodynamic and echocardiographic features of the right ventricle indicate that that muscle on which life is dependent is starting to fail. So, it’s a combination of where you are in the therapeutic algorithm and how the right ventricle and the pulmonary vascular bed is responding to that. So people who are end-stage are at the end of their therapeutic options and/or their RV is starting to show signs of failure.

Dr. Farber: Okay, Olivier, do you like that definition or would you change it at all?

Dr. Sitbon: No, I agree with Adaani. When she says about the no therapeutic alternatives, do you include lung transplantation withing the alternatives?

Dr. Farber: For me, lung transplantation is included into the treatment strategy.

Dr. Sitbon: Besides medical therapies, I think we have to consider lung transplantation in the therapeutic strategy, and for me a patient with end-stage disease, very advanced disease, is a patient without any indication for lung transplantation. I think if we have this option of lung transplant, we cannot say that it is end-stage disease, because for me lung transplantation—okay, that’s another disease, but I think that—

Dr. Farber: So, Olivier, you would consider a patient as end-stage as somebody who, for whatever reason, does not qualify for, or cannot obtain lung transplantation.

Dr. Sitbon: Exactly.

Dr. Farber: Maria, how do you see this? How would you view this as a transplant physician?

Dr. Crespo: Yes, I think I agree with Adaani. I think end-stage pulmonary hypertension should be considered in those patients who have failed all types of medical therapy and lung or heart-lung transplantation, is the only option for them. Mechanical circulatory support as a bridge for lung transplantation should be considered for those patients who have developed end-stage pulmonary hypertension and and refractory right ventricular failure.

Dr. Farber: For us, all being in Western Europe or the United States; I assume we would consider somebody who has not yet received systemic prostanoids not a failure or end-stage.

Dr. Crespo: Yes, that’s correct.

Dr. Farber: This is very interesting. As an aside and of interest to this discussion, I just returned from New York...
In meeting with physicians and patients there, it is clear that patients do not receive systemic prostanoids. They’re not available. So, in a locale like New Zealand in which systemic prostanoids are not an option (ERAs and PDE5-inhibitors are available), you would need to consider transplantation much sooner than you would in Pittsburgh, Paris, or Houston. Thus, much of the definition of end-stage disease may depend on what therapies you actually can access.

**Dr. Frost:** I’m surprised, given the socialized medicine in New Zealand, that they would consider a transplant a cheaper and more readily available option than aggressive intravenous therapy, but who knows?

**Dr. Farber:** That’s the current status there.

**Dr. Frost:** I’d like to try to address what I think was Olivier’s point, which was 2 things: number 1, they, (they, being the French) are very appropriately aggressive with early recognition and initiation of transplantation as a therapy option when they can see the train is coming down the tracks at them. Unlike the position that we are frequently in here (in the US), which is that we actually can’t get our patient transplanted until they are at the point where frankly, they are really bad transplant candidates. By the time our patients are on multiple therapies, IV drugs, and meet the criteria for the LAS exception, which requires deterioration on optimal therapy, and an elevated right atrial pressure >15 or a cardiac index of less than 1.8/L/m², quite frequently those patients are being transplanted at the point in time a) where their RV is already failing; b) they are likely to die waiting for the transplant; and c) their RV, compromised even if it does recover, is going perhaps best case scenario even if it does recover, is going to result in a stormier perioperative course and, because of that, a greater likelihood of primary graft dysfunction and the complications that are associated with transplanting truly end-stage PH patients. So I think Olivier’s point is very important. We need to think about it earlier, perhaps do it earlier. The hard thing is trying to find where the line in the sand is. Is that a paraphrase?

**Dr. Farber:** Why do the French look at this differently than we Americans do?

**Dr. Frost:** Maybe because they can get them transplanted earlier. We really have a terrible time... if you know that the patient has failed therapy after therapy and if the RV is looking bigger and the cardiac index is getting smaller, we still cannot get them transplanted, so listing them is moot if the Lung Allocation Score does not permit them to be transplanted. By the time it permits them to be transplanted, quite frankly, a bunch of these people are really almost too sick to be transplanted. We’re doing salvage therapy on patients who increasingly, embarrassingly, are at the edge where salvage becomes harder and the complications of transplant become more. I think the French, and possibly the Germans, too, Olivier you can tell me, are much faster about moving them down the transplant line, and they don’t have the same restrictions, I suspect, to getting them transplanted.

**Dr. Sitbon:** Yes, yes. I can give you some information about the system of lung allocations in France, in particular, for patients with refractory right heart failure in the setting of pulmonary hypertension. We have the possibility for those patients who are hospitalized in intensive care unit on the maximal medical therapy, including IV prosta-cyclin. For PAH on triple-combination therapy, including IV prosta-cyclin, refractory to this association, we have the possibility to put them on the very urgent transplant list, and those patients are awaiting for a graft for a maximum of 15 days. Usually those patients are transplanted within the time frame, so 15 days is the maximum listing for highly urgent list, and usually we are able to transplant them during this time.

**Dr. Crespo:** Olivier, were any of those patients on ECMO?
Dr. Frost: You know, I have had patients in the ICU for a month-and-a-half and not been able to get them transplanted.

Dr. Farber: Yes, we have had the same problems.

Dr. Frost: Partly, what we’re doing is we’ll admit inpatients into the ICU. We know they’re at the end of their medically managed therapeutic options; they are requiring frequent hospitalizations as we start an inotrope to increase their LAS score and help to get them transplanted. At this point, they’re having multiple admissions, their kidney function is starting to deteriorate, but the minute they start showing features that identify them as high risk, it can actually count against them. So worsening parameters of disease are associated with worse post-transplant outcomes. Then their Lung Allocation Score is skewed against transplant, so we are really in a very bad position. The European treat-to-goal paper demonstrated very nicely that moving people down the algorithmic tree of therapy very briskly based on achieving milestones, such as inadequate walk, the resolution of functional class 3 to a functional class 2, and MVO2 etc., and adding therapy including transplant to achieve those goals resulted in better survival. It would not be possible in the US to get a patient transplanted who is a persistent functional class 3 and a walk that was less than 300. So we end up then with people with deteriorating renal function, passive congestion of the liver, liver compromise without a transplant option—and it’s a huge issue.

Dr. Farber: Maria, I would assume that the French and UPMC are using very similar criteria for transplant eligibility.

Dr. Frost: Doesn’t sound like it.

Dr. Farber: It doesn’t sound like it, exactly. And I agree, it does seem that it takes longer in the US to get PAH patients considered for and/or transplanted than it does in Paris. Is that true? If so, how do we fix it? Does it make a difference? Seemingly, it does.

Dr. Crespo: The February 2015 revised LAS scoring system includes measurements of heart function and heart failure that will result in a more accurate predicted risk of wait-list mortality in patients who have pulmonary hypertension so patients who have PH are expected to have higher LAS, increasing to 90% percentile in some patients with PH and right ventricular failure. I think it’s very early to assess the impact of the new revised LAS changes on survival in patients with PH before considering adding other values like ECMO and other markers of poor outcome.

Dr. Frost: I mean the concept that in our patients who are on as much therapy as we can reasonably give them, do not really enter into the transplant arena until they have a right atrial pressure of 15 or greater or a cardiac index of less than 1.8. At that point in time, when you have no other therapies except transplant, the concept that this is the point in time that you are listing them is the antithesis of the approach, for instance, of renal transplant, where the earlier you can do the transplant the better–people are being preemptively listed before they’re even dialyzed now. And that is where they show the greatest, most valued both quality of life improvement, health care dollars improvement, and the highest survival rate, but we’re doing the exact opposite of that in lung transplantation in the United States. We are skewing the curve to the point where either people can’t get transplanted, or the ones who are getting transplanted are such breathtakingly high risk that the incidence of primary graft dysfunction, early rejection, bronchiolitis obliterans, death within one year, are all stacked against the PAH patient. There’s something very wrong with this system.

Dr. Farber: If that’s true, how do we change it?

Dr. Frost: Well, the lung transplant—the United Network of Organ Sharing and the fact that lung transplant is a Medicare-approved, Medicare-funded process means that they’re only gonna respond to data, and I think there’s been a lot of data generated from UNOS/OPTN that was incorporated to even get them to produce the modifications in the Lung Allocation Score to provide us with the meager exceptions we have, but I think that maybe it’s time to go back to the drawing board. You know, Olivier, Marius Hoeper, and a lot of European researchers particularly have done a lot of work looking at predictive markers of RV dysfunction which are indicative of the point in time at which the RV kind of reaches the point of no return, and what predicts the rapid evolution of that point of no return, the point at which the RV is so dysfunctional that the patient’s risk of mortality and secondary organ dysfunction, like liver, kidney, etc., starts to occur with a greater likelihood. That is what we need to have and we need to be able to take that to UNOS and say these are more reasonable early predictors of mortality. We are currently skewing the likelihood of death with the transplant by transplanting people who are much too sick. So data are what we need, and that means things like biomarkers, echocardiographic markers, in a more scientific way than we’ve been generating today.

Dr. Crespo: I agree, yes.

Dr. Farber: I would agree, especially given the seeming disparity between the two sides of the Atlantic. How do we generate these data; they should be available?

Dr. Frost: If you look at the data on lung transplants for PAH patients, if they survive beyond a year, they do great, but the greatest risk is within the first six months post-transplant and the survival statistics at their centers might not actually help provide us with the data that we need to be able to assess if and where US PH transplant indices can be improved. My sense is that in the US we are either disenfranchising PAH patients or we’re transplanting people too late in the course of their therapy, and I think that the European data might inform us. Olivier, do you publish your own transplant data, or do you put it in ISHLT where it’s either sporadically entered or diluted out by other centers without your level of expertise?
Dr. Sitbon: I think all our cases are included in the statistics of the interventional statistics for following transplant, and the results we have in patients with PAH are about similar to that was observed in other centers, so the survival after lung transplant is worse than for the other indication, than lung transplant for the other indications. It is shorter during the 6 months; first 12 months, the mortality did increase in those patients. However, if we are not doing lung transplants in those patients, the spontaneous survival is very, very poor. So that’s why we decided to put pulmonary arterial hypertension at the top of the list for lung transplantation besides refractory lung fibrosis. For example, in our center, we never transplant patients with emphysema, never. We consider that the spontaneous outcome of those patients is similar to the outcome with a transplant. So we really think that lung transplant is a very important option for patients with pulmonary arterial hypertension and also for patients with—and in particular patients with—pulmonary veno-occlusive disease. But we know that the results are worse after, but if we are waiting for at least 1 year, the results after 1 year are similar to the other, so we have the same result as in other centers.

Dr. Farber: Okay, since we brought up the topic, let’s talk about mechanical support for the right ventricle: ECMO, RVAD, or any other device. Where do we think we are with these devices? Do we use them at all, do we use them strictly as a bridge to transplant, or do we consider their use as a bridge to treatment? In sum, how do we currently view any of these devices and their use?

Dr. Sitbon: Okay. Today we consider this kind of support, ECMO, or mini ECMO, only for bridging patients to lung transplant. I know that to use this kind of system, ECMO for example, to recovery or waiting for the efficacy of drugs could be an interesting approach, but I think that today no one or almost nobody has the experience of that. I discussed with Marius Hoeper a few months ago about that. I think he used this kind of technique only in 1 patient as a bridge to recovery not bridge to lung transplantation. But now with the use of first-line combination therapy, they are very, very quickly efficacious and I think with this kind of approach of first-line combination, I am not sure that we need really mechanical support awaiting the efficacy of drugs. For the other patients, patients already treated with two or three drugs, including prosta-tacyclin, I think if we consider mechanical support, this can be done only in patients awaiting lung transplants. That’s my point of view.

Dr. Crespo: Yes, I agree. We use ECMO on patients who have developed end-stage diases, as a bridge for lung transplantation. We use ECMO support in selected patients with profound respiratory failure secondary to lung disease and refractory as a bridge for lung transplant.

Dr. Frost: There’s what we do, and then there’s what is discussed in the literature, and we’ve used VV-ECMO for people who have decent sized right-to-left shunts where their RV is failing and they are hypoxic because it’s much less invasive than veno-arterial. We’ve done veno-arterial ECMO more frequently, but it is still rare; and if we can’t get them very quickly to transplant, our results are not good. Dr Shaf Keshiavee has published an aggressive management protocol in Toronto with patients who were failing with pulmonary hypertension. They’ve reached the end of—as I understand it, they’ve reached the end of their therapeutic algorithm, they’re still in marginal heart failure, there’s nothing else that can be given for them, they’re listed for transplantation, and this is ECMO as a bridge to transplant and just a Novalung. Most of the data, as Olivier alluded to, I think, about a bridge to recovery, and in this instance the North American data, is not very good. I think Erika Rosenzweig published a paper looking at outcomes of PH patients with potentially reversible disease where ECMO was used as a bridge, but the results were dismal. I don’t think there were any long-term survivors. There were a few short-term survivors—people who survived to removal of ECMO, but did not survive the hospitalization. The same was not true, as Olivier alluded to, for the bridge to transplant, where it was a very successful intervention that allowed a patient to survive to transplant. The role of RVADs in the future, however, is unclear to me. We’re clearly very bad at figuring out when the RV is failing, so to do a bridging maneuver with a VAD, which has its own complications (hemolysis, the operation itself) and importantly you have not dealt with the afterload of the right ventricle, you’re just putting in a stronger pump. This is fraught with questions. When RVADs have been laced they have not been terribly successful. I think putting in a VAD when you haven’t done anything about the afterload is probably as useless in RV failure as it is in LV failure. I mean, you have to have somebody optimally treated if their left ventricle is failing and the LV is still bad before you put in a VAD or a total heart for that indication. You don’t put it in somebody with uncontrolled systemic hypertension. So I guess the point is that we’re skewing the results for any utility for right ventricular assist devices for pulmonary hypertension because of our own inability to appropriately reduce the resistance in the pulmonary vascular bed, so I have no idea what will be the role of our outcome of RVADs in the future, in future management of PH.

Dr. Farber: So, Olivier, in regard to Adaani’s last question, is there any future for RVADs in PH, and if so how would we do this?

Dr. Frost: You get the easy questions (laughter).

Dr. Sitbon: Easy questions. The future for RVADs, that is the question? I think today we cannot consider RVADs outside of bridging to lung transplantation. Maybe if we can miniaturize. . .

Dr. Sitbon: The system could be an option if you want to consider this to recovery awaiting the efficacy of drugs, but today we have too much complication with the system to consider this kind of approach in patients without any surgical options.
Dr. Farber: Maria, what do you think?

Dr. Crespo: There’s not much data on the efficacy of RVADs on this condition. We haven’t used right ventricular assist devices in refractory and/or end-stage PAH with RV failure.

Dr. Farber: I think the main point is that Adaani has made: just sticking an assist device into a ventricle without somehow changing the resistance of the pulmonary circulation is unlikely to be successful. And if we define somebody as refractory PAH because we can’t control their resistance, I don’t really understand, at least currently, how an assist device is going to be beneficial. Moving on to a few other topics: Olivier, do you use or perform atrial septostomies?

Dr. Sitbon: No, no. Usually we don’t use atrial septostomy. We sometimes indicate the Potts surgery for children and we have very good results in children with suprasystemic pulmonary hypertension.

Dr. Farber: Right, you have published on that.

Dr. Sitbon: And we have very, very nice results with the Potts surgery and recently we had two cases of not children, but teenagers, who had not the Potts surgery but Potts intervention via endovascular—

Dr. Farber: We’ve done some of those, too.

Dr. Sitbon: And it was successful in 2 teenagers. I think it is a quite difficult intervention, endovascular intervention, but it seems that the results are very, very good. In all patients we did Potts surgery, we were able to wean off epoprostenol.

Dr. Farber: Adaani?

Dr. Frost: We’ve done some septostomy. Because we’re affiliated with Texas Children’s, there were a fair number in the pediatric patient population up into early adulthood. In addition, under my watch here in adults, we did 2 or 3. The first one failed acutely due to hypoxia. The concept of multiple sequential mild dilations had not been reported. Another anorexia-associated PAH simply wasn’t sufficient to benefit the patient. In contrast, the data from Julio Sandoval is spectacular, reflecting the level of his expertise, and that is not something we’ve been able to reproduce.

Dr. Farber: The other subject I would like to discuss is palliative care for these end-stage patients. When should we do it? How do we do it? Do we do it enough? Are we afraid to do it because of some of us it seems as if we are giving up? How do we go about making it better? I’ll start with the Americans and then let Olivier have the last word. For example, these are patients that have end-stage disease, have received all possible medical therapies, either don’t qualify for transplant for whatever reason, and seemingly there is no alternative remaining. Somehow, many of us always think that there may be another treatment because we find it difficult to admit that we cannot do anything else (in a way that we are defeated). How do we deal with this?

Dr. Crespo: All patients who come for lung transplant evaluation are being evaluated by palliative care. This has been very beneficial helping patients cope with their disease and prognosis. This approach has also helped prepare patients and their families with end-of-life decisions.

Dr. Frost: You know, maybe you’re better at it than we are, Maria, because you have this built in sort of palliative care initiative with your transplant program, but to PAH patients it’s a difficult subject to broach. Interestingly, I never have much push-back from transplant patients if they were told they weren’t transplantable, but there is a fair bit of resistance with the PAH patients. I think it’s maybe because they were at time of diagnosis told that they had a horrible disease with a high mortality, and yet many of them have lived two, three, four times their projected lifespan, and they’ve done that because the drug evolution has been such in the last 15 years that just as they reach the end of one drug’s maximum effect, another one has come along to sort of bail them out, and I think that the number of studies, the number of new drugs, the fact that so many of them have survived already against the odds that are huge actually has proven to be an interesting but difficult issue. It makes them very willing to go into a study, but I think it makes them a little unwilling to accept their own mortality. The ones who do are quite often older and are simply tired of being sick. For younger patients, it can be brutal for them, particularly if they have survived to see their children grow into early adulthood and they have expectations now that the science will continue to stay one leap ahead of their disease. So to answer your question, I think that we’re bad at palliative care, I think there are some things that are unique to our patient population. I do two things when I start a patient on an IV drug. I refer them for transplant because I know it’s my last and best drug, and I will quite often start talking to them about palliative care, what are we going to do if; if they’re turned down for transplant and if this drug doesn’t work, and it does not seem to have made my issues or the patient’s issues any easier or any smoother.

Dr. Sitbon: I think that patients with end-stage disease or refractory right heart failure without an indication for transplant or because it’s not possible have the same picture that we are doing for patients with cancer—the question for those patients is what is the, how do you say that, the level of treatment we have to apply, we have to push the treatment up to what kind of level? What are our expectations? If it is really end-stage disease, if we don’t have any option for them, I think that the question of down-titration of drugs have to be addressed because we know that we have patients with a lot of side effects with very high-dose epoprostenol, for example, and they are refractory to these kinds of treatment and we have no other option, so what are the maximum levels to reach in those patients. It’s exactly like for cancer. In a patient with cancer, we try chemotherapy, then a second one, then a third, and what is the next option. Well usually we don’t know, and we consider palliative care in those patients, and I think it’s exactly the same for patients with PAH. They both are very similar diseases.
Dr. Farber: Okay. This was a terrific session. Does anybody have any last words they’d like to add or anything that we missed?

Dr. Frost: I’m sure we missed something (laughter).

Dr. Farber: Only lunch—(laughter).

Dr. Farber: Adaani, Maria, Olivier, thanks a lot. I appreciate your time and effort. This was such a worthwhile discussion of a very difficult topic.

NEWS TO USE

Help improve your PH patients’ access to their prescribed treatments.
The Specialty Pharmacy Feedback Form—an initiative of PHA and the Caring Voice Coalition—provides an opportunity for you and your patients to let SPs know what they’re doing well and where they can improve. Input from medical professionals helps the Specialty Pharmacy Advisory Board identify trends and best practices in the specialty pharmacy field. Submit your comments at: www.PHAssociation.org/SpecialtyPharmacyForm.

Help ensure PH care for all!
Support your colleagues as they seek to identify additional barriers encountered by underrepresented minorities and socioeconomically disadvantaged patients seeking PH diagnosis and treatment. Please take our brief survey, as the committee seeks to identify the populations most affected by these barriers, as well as the barriers themselves. https://www.surveymonkey.com/r/PHCareforAll

About PH Care for All:
Progress in treatment of pulmonary hypertension (PH) and the organization of the PH community has been substantial over the past 25 years. The PH field has progressed from zero treatments to 14, which is as many or more than all but 2 of the roughly 7,000 rare diseases. Medical research and knowledge in the field is expanding rapidly.

Early data collected through PHA’s Envelope of Hope program is beginning to show that PHA’s Early Diagnosis Campaign is making headway in terms of the average time from onset of symptoms to point of diagnosis; however, research findings presented at the 2014 meeting of the American Thoracic Society by Cardenas-Garcia et al indicate that underrepresented minorities and socioeconomically disadvantaged patients are impacted disproportionately by the most common barriers to PH diagnosis, as well as by a number of additional barriers unique to these populations. These barriers not only adversely affect the PH diagnosis itself, but also impact patients’ ability to receive treatment once the diagnosis has been made. With preliminary data indicating that these patients experience diagnostic delays beyond the mean of 2.8 years indicated by REVEAL, the concern is that many of these patients are missing the window for treatment and intervention entirely. As PHA continues to positively impact the average time to PH diagnosis, we must ensure that the additional needs of ethnic minorities and socioeconomically disadvantaged patients are met.

From this desire, PH Care for All was born. The committee, consisting of 23 expert clinicians and academicians committed to reaching these vulnerable patients, is led by Vinicio de Jesus Perez, MD, and Arunabh Talwar, MD. With this initiative, the PHA continues its commitment to advocating for PH patients by educating health care providers and building a foundation for new health policies that will favor this vulnerable patient population. Our ultimate goal is to ensure that all PH patients receive the same level of care regardless of ethnicity, socioeconomic status, or race. In short, we’d like to ensure PH care for all!

Start a support group at your practice!
Hundreds of PH-treating physicians and allied health care professionals play a vital role in the success of PH support groups. Support group participation helps with patient compliance, as patients learn about the disease, gain coping skills, and find the emotional strength to keep fighting.

According to our latest census, which surveyed 160 leaders, half of our support groups meet in hospitals or clinics. Nearly 60% of meetings have speakers, 82% of which have a medical background. As a medical professional, you have the resources groups are looking for: a meeting space and expertise. Let PHA do the rest, providing food sponsorship and publicity. Start a support group at your hospital or clinic by contacting MichaelK@PHAssociation.org today.