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The Treatment Algorithm in the New ESC/ERS Guidelines

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Dr. McLaughlin:
Hello and welcome to this segment of, MedEd On The Go. We're going to talk a little bit about the new ESC/ERS Guidelines and specifically the treatment algorithm. I'm Vallerie McLaughlin from the University of Michigan and I am joined by my dear friends and colleagues, Dr. Richard Channick from UCLA and Dr. Ioana Preston from Tufts in Boston. Welcome guys, I'm really excited to have you.

Dr. Preston:
Thank you, Val.

Dr. Channick:
To be here.

Dr. McLaughlin:
So, the new guidelines came out in August of 2022, the first guidelines since 2015 and one of the newer documents since the World Symposium in 2018. Some really good information, a little bit of information about adjustments in the hemodynamic definition, some tweaks in the classification, but what we're really here to talk about today is the treatment algorithm. And as you all know, we are treating pulmonary arterial hypertension more aggressively these days, lots of great evidence with combination therapy. But this treatment algorithm really highlights some of the changes in the demographics of patients that we see. If you look at the algorithm, it pulls off patients with comorbidities to the right. And gosh, don't we see that in clinical practice? It's not like the days of the NIH registry in the 1980s. Ioana, you want to talk a little bit about what we've noticed in more recent registries regarding comorbidities?

Dr. Preston:
Yes, Val, these guidelines highlight the fact that the pool of our patients has changed. You know, in the 1980s and early 1990s, we used to see young patients with severe PAH, with really no comorbidities and severe RV dysfunction. Now, the registries from both the United States and Europe and worldwide, teach us that the demographic of patients with PAH group one has changed. They are older, they have a significant more comorbidity such as hypertension, obesity, coronary disease, also lung dysfunction. So, the comorbidity aspect of these patients has become very important in deciding their treatment algorithm.

Dr. McLaughlin:
Yeah, absolutely. And if you look at some registries, you can kind of cluster patients into kind of the pure PAH, like what we saw in the 1980s and 90s, and then more of a lung phenotype and more of a heart phenotype. Rich, you want to elaborate on that?

Dr. Channick:
Yeah, that's a great point, Val. And it really does get to, I think they we're diagnosing pulmonary hypertension more and more

aggressively, which I think is a good thing, but we're also identifying these different subtypes and I think underscoring that there's some gray areas. So, you know, when we talk about a lung phenotype, we're talking about a patient who does have pulmonary arterial hypertension as we define it hemodynamically, but also may have some lung disease or, you know, abnormal lung parenchyma, but not to the degree where we'd say the PAH is due to the lung. And same with the heart phenotype, where there may be older patients they have some degree of diastolic dysfunction, very common cardiac conditions, but they have pulmonary arterial hypertension. But as Ioana alluded to, that's not the same as, you know, a 30-year-old patient, you know, with pure PAH. So, we are starting to see these gray areas or various types within the broader group.

Dr. McLaughlin:
Yeah, and you know, one thing that brought this to light actually was the AMBITION study, right? If you remember, the adjudication committee of the AMBITION study started saying, you know, gosh, there's a lot of patients here with these comorbidities, and that led to an amendment in AMBITION to exclude patients with multiple comorbidities. Although when you look at those patients, they did benefit from therapy, you know, just not as robust of a benefit. So, I think all these things contributed to the ESC/ERS Guideline panel saying, you know, gosh, maybe we should be a little bit more reserved with treatment in these patients with comorbidities. And they pulled that out to a box on the right of the treatment algorithm, but, you know, perhaps that's a little bit of an oversimplification. What do you think about that, Ioana?

Dr. Preston:
Yes, Val, I think from the AMBITION trial as you alluded to, we've learned that even patients with PAH group one who do have significant comorbidities, benefit from the combination therapy. Do they have maybe slightly more side effects? Maybe. Do they have slightly less of a magnitude of a benefit compared to the pure PAH patients? Yes. However, they did benefit from combination therapy. So, I think the guidelines try to alert us to identify patients with significant comorbidities. And even though we could, and we should consider combination therapy, we need to be aware of the side effect profile and the possibility that the presence of comorbidities may bring up other issues during the treatment.

Dr. McLaughlin:
Yeah, great point, Ioana. Now, Rich, let's just talk about this very generalized comorbidities. And you know, to me, you know, there's a lot of clinical judgment that goes into this, right? Like, I don't think you can lump all comorbidities together. You know, there's the number of comorbidities, there's the severity of the comorbidities, and then, of course, you need to put that in context with the PAH phenotype. It's one thing to have three comorbidities and a PVR of 3.5, it's another thing to have one comorbidity in a PVR of 10. Do you want to expound on that a little bit?

Dr. Channick:
Yeah, no, absolutely Val. I mean, I think the bigger point is that, you know, this is not simple, and you can't simplify it into an algorithm or a guideline, and these patients are a continuum and comorbidities are a continuum. So, the mere presence of a history of hypertension doesn't mean you're not going to respond to combination therapy if you have significant pulmonary RT hypertension or well-controlled diabetes is not going to mean that you're not going to respond to combination therapy. But I think the concept is that this phenotype with multiple cardiac and other comorbidities, atrial fibrillation, uncontrolled hypertension, morbid obesity, that may identify a phenotype that may as, Ioana says have poor tolerance from PAH therapies and maybe less benefit. And those patients, you do need to be more cautious. But you know, every case is different.

Dr. McLaughlin:
Right. You know, to shine some color on this, let's just give a couple of examples. You know, as we discuss comorbidities are common, our phenotype has changed, you know, you might say on one end of the spectrum and I'm just going to give extreme examples, on one of the spectrum you might have a 75-year old woman with hypertension, diabetes, A-fib, obesity, who is well diuresed at the time of her calf, and on her calf has a wedge of 14 and a mean PA pressure of 27 and a PVR of 3.5, and her RV is normal on echo. You know, that's one end of the spectrum that, you know, they meet the letter of the law in terms of hemodynamic definition, but not the spirit. Like that is a cardiac phenotype that I think at least I would treat a little more conservatively, you know, after optimizing the other medical illnesses maybe monotherapy, probably with a PDE5 inhibitor, and probably a little reluctant to escalate therapy. What do you think about that?

Dr. Preston:
Yeah, I totally agree, Val. This is one end of the spectrum and we do see these kind of patients in clinic. However, let's say that this patient who is 75 has scleroderma, has hypertension, has coronary disease, maybe one vessel that has a stent and it's opened and not active, you know, ischemia. But she has a PVR of five or six wood units and minimal lung parenchymal involvement. And that I would treat as a group one PAH even though she has comorbidities, I would consider her for combination therapy. So, this is where the gray zone is and I think the algorithm that is proposed in the newest guidelines, are overly simplified and we really need to dig deep into

understanding exactly where these patients fit.

Dr. McLaughlin:
Yeah, I think that's a great example of kind of middle, lots of clinical judgment required. That's a great example, Ioana. And then on the far other end of the spectrum, you might say, you know, there's a 45-year-old woman with heritable disease and, you know, we're in the US, let's say she has obesity and hypertension, but she's heritable, she's got severe RV dysfunction, her PVR is 10. I mean, I would treat that just the way I would a clear-cut group one PAH with aggressive combination therapy.

Dr. Preston:
Or even infusion therapy

Dr. McLaughlin:
Yeah.

Dr. Preston:
if her hemodynamics and functional class are severely impaired.

Dr. McLaughlin:
Yeah, so I think there's a great discussion. I think sometimes it's hard to go into all the details and nuances when you're trying to make a figure, you know, for the masses. And so, these important points that you both are making, I think are really critical and judgment is required with each case before we just say comorbidities get monotherapy. Rich, any parting comments you want to make?

Dr. Channick:
Yeah, I think that the other point is that just because an algorithm recommends monotherapy, doesn't mean that you have to necessarily keep that patient on monotherapy. And I think as we know, this is a dynamic process. And so, as you may start monotherapy cause you're careful looking for side effects, but if a patient continues, for instance, to be diuresed, and continues to be symptomatic and not meeting treatment goals, there's nothing to stop you from adding additional therapies. I think the concept is, you know, to be cautious in those patients which I think is reasonable.

Dr. McLaughlin:
Yeah, I think it's a really great point. I think the point here is, the issue is more complex than just the branching of an algorithm. And I'm so thankful there're experts like the two of you that are out there treating patients and teaching about this. So Rich, Ioana, it was really wonderful to talk to you about these guidelines. I'm sure we'll have many more conversations about the guidelines in the future. And thanks to the audience for joining us.

Dr. Preston:
Thank you.

Dr. Channick:
Thank you.

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