[MUSIC PLAYING]

STEPHANIE MAXIMOUS: These year-end reviews are very difficult to prepare for because naturally there's been hundreds of articles that have come out. So this is a little bit of having spoken with folks about what they thought would be interesting to talk about. And obviously, we can't cover everything. But these are some of the things that have come up also in conversation with some of the trainees. And I'm happy to also talk about other topics towards the end if there's any additional questions.

So we'll break it down into the first half, we'll do some pulmonary topics, but focusing specifically on smoking-related lung disease. So we'll talk about COPD, both triple therapy, a few studies that have come out in the last year, as well as the endobronchial valve program that's being led here, UPMC, as well as some updates in immunotherapy and lung cancer. And then we'll transition to a couple of studies in critical care that have generated a lot of buzz, and we'll talk about some of the limitations with those.

Hopefully, by the end of this hour we'll be able to identify benefits of triple therapy as compared to just the monotherapy or ICS LABA combinations. We could talk more about the utility of immunotherapy in the treatment of advanced non-small cell lung cancer. Hopefully, we'll be able to understand the role of endobronchial valve placement for lung volume reduction. And we will be able to describe the limitations of a couple of studies looking at vitamin C and balanced crystalloids in critically ill patients.

So before we jump into all of that, I did want to highlight one paper that came out right at the end of the year. This is a report that came out in the annals of the American Thoracic Society. And this was generated by a group of pulmonary critical care division chiefs that got together at the American Thoracic Society in 2017 in Washington, DC, to focus specifically on the gender disparities going on within our subspecialty. We know that this is an issue broadly in society, as well as throughout medicine. And PCCM is no difference.

And so what this group did was they looked at a survey that had been generated by the ACGME prior to this meeting that identified five different topics, and they came up with a list of ideas for how to approach these issues. Those five main topics were gender climate, which includes implicit and perceived bias for things as varied as career development award grantees, medical student evaluations of faculty and employment; disproportionate burden of family responsibilities among women faculty, so that's referring to things such as the second shift, which is of all the tremendous amount of work that a lot of women have to do after they leave their paying job, as well as discrimination surrounding maternity leave, breastfeeding, pregnancy; the lack of women at senior academic rank or in leadership positions, so for example, we know that pulmonary and critical care fellowships across the country have about 30% women at this point, but program directorships have about 20% women, and division chiefs have about 15% women. So we are leading the charge currently since Dr. Morris is our interim chief, but they talked a lot about how to foster more of that leadership. And then lastly, retention of women, this idea of the leaky pipeline when values don't align at work and at home, as well as the lack of gender equality and compensation.

So they came up with some ideas for how to approach these things at the national organization level, at the institutional level, and at the individual level. And we'll be interested to see how this all plays out.

All right, so getting into the papers. So thinking about COPD, the current guidelines that were generated by the GOLD society in 2017 really helped organize a little bit patients based on their spirometry, their severity of exacerbations and frequency of exacerbations, and severity of symptoms, and helped to clarify the pathway with which we decide what kind of medications we're prescribing for these patients.

But a lot of this comes from expert consensus as opposed to being rigorously studied, especially in terms of comparing different drug strategies against each other. And so what we've seen in the last 18 months or so is this idea of fixed triple therapy that now exists in a single inhaler design.

I think this is important because we know that patients in general, when it comes to medication usage, it's very difficult to get patients to use their medications. In a survey that was done looking at insurance coverage of inhalers, they found that only maybe 41% of patients were even picking up their inhalers, let alone knowing how to use them, using them on a regular basis. So I think anything that can be done to lower the barrier to inhaler usage, particularly for our sickest patients, is probably something worth looking into.

And so what a lot of these studies did is focusing on this group D GOLD group, which are those who have severe COPD based on spirometry, increased number of exacerbations, and higher amount of symptoms, and looking at how this idea of using the fixed triple therapy, which is a combination of inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting beta agonists, might be able to improve certain outcomes in these COPD patients.

So one of the studies that came out was the Trinity study, which specifically was looking at triple therapy versus monotherapy with a long-acting muscarinic antagonist, specifically tiotropium. So what they did was they looked at over 2,500 participants who had severe COPD by spirometry and had at least one moderate to severe exacerbation in the prior year and severe symptoms by their CAT score. And what they were focusing on was their exacerbation rate after about a year.

And what they found was that the fixed triple therapy, meaning all the three medications in one combined inhaler, was associated with a 20% reduction in exacerbation rate compared to long-acting muscarinic antagonist alone. So note that that was comparing a little bit apples to oranges. But they also did compare it to the open triple therapy, which is what we're more commonly used to using, like a dual ICS and LABA combination plus a long-acting muscarinic versus the long-acting muscarinic alone, which performed similarly.

So what the folks in this study did was said, OK, well, it seems that the fixed triple gave us improvement over the long-acting muscarinic by about 20%, as did the open triple therapy, so hopefully, those two things will perform similarly when compared to each other. In secondary analysis, they did look at FEV1 improvement, and they also found that the fixed triple therapy was superior to the long-acting muscarinic alone, and also was not inferior to the open triple therapy and adjusted mean change in FEV1.

So the take home points from this study, as well as a similar study that looked at just the combination long-acting beta and ICS combination support the effectiveness of triple therapy, specifically an exacerbation reduction compared to long-acting muscarinic alone, or the combination long-acting beta and inhaled corticosteroid regimen. They found that the fixed and the open probably had about similar impact on COPD outcomes.

Now challenges with this, though, is that they were using double dummy placebos. But in that case, you're not able to truly prove that one patient-- patients will know if they're using two drugs versus one drug, right? So it's a difficult thing to actually design a study around, to actually show that one inhaler alone is going to be better than the two inhalers because of physical challenges.

And in this study, the generalizability is a little bit challenging as well, because this study was done in the UK. They had a kind of outstanding medication adherence, greater than 94% in all the groups, which is somewhat unheard of. And as well as their LAMA dosage is a lot higher than what we commonly are used to using here. So a couple of barriers towards perfect generalizability compared to a general US population, but something that may help us think a little bit more about how to use this triple therapy fixed combination in our severe COPD patient population who keeps coming in with repeated exacerbations.

Another study that looked at a different combination, LABA ICS in this case, was the FULFIL trial. So in this case, they were looking at this, again, fixed triple therapy in one inhaler versus twice daily ICS LABA. And in this group, they had a little under 2,000 symptomatic patients who were a different patient population than what we saw in the prior study. So while they still had high amount of symptom burden and their FEV1s may have been less than 50%, they also included somewhat of a more moderate COPD group with FEV1 50% to 80% and frequent exacerbations.

So this group of patients didn't all fit into that GOLD class D group. So keep that in mind. But they did follow this group out for 24 weeks and then they had an extended sub-study out for a year. And their primary endpoint in this case, as opposed to exacerbation rate, was change from baseline FEV1 and St. George's respiratory questionnaire total score, which they used as a surrogate for quality of life.

And what they found in this study was also that the FEV1 was improved in the fixed triple therapy as compared to the combination LABA ICS. And that was also present when they looked at this smaller group out for one whole year.

Their exacerbation rates in general were pretty low, and that's probably because of this somewhat more moderate group of COPD patients that they included. But they did find, even within that, they found that there was a relative reduction of about 35% with triple therapy compared to the LABA ICS combination.

And as far as quality of life was concerned, they really only detected a significant difference when looking in the short term group. So within 24 weeks they did find a difference in the St. George respiratory questionnaire, but that was not statistically significant out to 52 weeks.

So the take-home points from this study suggest a benefit, again, of fixed triple therapy over just the LABA ICS combination in lung function, although not very clear if there is benefit in quality of life. Note that this cohort was more similar to maybe a GOLD class B disease with less frequent exacerbations.

And since these studies have come out as well as several others that were included in a meta analysis that came out in late November that kind of said the same thing, that the fixed triple therapy is showing improvements in exacerbation especially, the GOLD guidelines have not yet changed. Because note that in our rubric here from the 2017 guidelines, there is this pathway that we should be considering using triple therapy when our patients are having frequent exacerbations.

I think this box gets very confusing, right? I think when we have a lot of patients who keep coming into the hospital, more and more medications keep getting piled on top. But I think hopefully with simplification of the actual inhaler regimen, we might see some studies that come out telling us if that's actually impacting patients over the long term.

All right, so let's transition to talking about lung cancer immunotherapy, staying on the theme of smoking-related lung disease. So I think this is the age of-- if Mark Gladwin was here, he would say that this is the age of precision medicine and using genetics to really think about individual patients. And I think the changes that are happening within lung cancer is a great example of that.

So one example is when thinking about the role of immune checkpoint blockade for restoration of T cell-mediated antitumor immunity in advanced non-small cell lung cancer. And what we mean by that is looking at PD-L1 and PD-1 inhibitors.

So as a reminder, hopefully this cartoon will show us that on the surface of the tumor cell, we have PD-L1 programmed death-ligand 1 expression, and on the surface of our T cells, we have PD-1 expression. And when these combine together, it inactivates the T cell's ability to have antitumor properties. So now we are having increasing numbers of agents that are able to target either the PD-1 on the surface of the T cell or the anti-PD-L1 on the-- sorry, the PD-L1 on the surface of the tumor cell to allow our T cells to do what they should be doing against these cancer cells.

And so we have a little bit of new data coming out about the efficacy of some of these newer drugs. So durvalumab is a monoclonal antibody against PD-L1. And so in this multicenter RCT, they were looking at if adjuvant therapy with durvalumab versus placebo could prolong progression-free survival among patients with unresectable stage 3 non-small cell lung cancer.

So what they did was there was a total of a little over 700 patients, most of whom got the study drug, and they were supposed to receive it within six weeks of receiving their chemotherapy, standard chemotherapy and radiation therapy, and continue for a year out or until disease progression or severe toxicities that caused them to change their regimen. And of note, they did not require these patients or participants to meet a certain threshold of PD-L1 expression. So they kind of included all comers. And they did test for PD-L1, but they didn't discriminate against who could or couldn't get the drug.

And what they found was that progression-free survival was significantly longer with durvalumab versus placebo. 17 months versus five months, which is pretty significant, especially compared to a lot of the other drugs that have been compared. And this improved progression-free survival existed in all subgroups, including those who had low PD-L1 expression.

They also had increased median time to death, or distant metastasis, with a significant difference between 28 months in the study drug group versus 16 months in the placebo group. Note that, of course, adverse events were common in both arms, not surprisingly, although there were more grade 3 to 4 adverse events in the group receiving durvalumab, specifically immune-related outcomes, such as pneumonitis and hepatitis.

So, I mean, things to take away from this study is that, in general, prognosis is pretty poor for standard platinum-based chemotherapy and radiation for a locally advanced, unresectable non-small cell lung cancer. Maybe only about 27% of these patients will be alive after three years. But adding some of these drugs that actually have somewhat manageable adverse event profiles might add more quality and length of time for them to have a progression-free survival.

In this group, about 40% of the participants had PD-L1 expression, less than 25%, which is interesting since we would have thought maybe that this drug would only be effective in those who have high PD-L1 expression. So this drug may also have high utility in a wider group of patients than initially thought.

Other news in the lung cancer world is looking at EGFR mutations and newer third generation drugs here. So one of the issues in the patients who are treated with tyrosine kinase inhibitors for lung cancer that has EGFR expression is that they may develop resistance to those first generation tyrosine kinase inhibitors. And so these later generation ones have been added as second and third line agents to take over when the first line agents are no longer working and these patients display disease progression.

So in this study, they compared osimertinib versus the first generation tyrosine kinase inhibitors for these patients who were untreated. So they were giving it to them for the first time as opposed to cycling it through as a second or third line therapy.

So what they found in these patients is that this third line or these newer drugs, osimertinib specifically, showed improvement in progression-free survival compared to the first generation, specifically, about 19 months versus 10 months improvement in disease progression or death. And they also displayed fewer serious adverse events, specifically 34% of those in the osimertinib group had grade 3 to 5 toxicity, versus 45% in the first generation group.

So this helps us to think a little bit more about maybe it's time to start using these newer drugs actually as first line therapy. Now that presents us with the question of, are patients going to form resistance to these newer drugs as well, and then we're just going to end up in the same cycle of needing to put patients back on a different drug once they stop responding? And I think we don't know the answer to that yet because this is just an interim analysis. And so we have to wait and see.

All right, so lastly, within the pulmonary section of this discussion, I wanted to introduce this idea being sort of spearheaded by Dr. Frank Scherba here of the Zephyr Endobronchial Valves. So thanks to him for sharing his slides that he has presented at other national meetings in the past.

So specifically, I think we're used to thinking about lung volume reduction surgery as being useful in patients who have very severe emphysema that is heterogeneous, that it takes up a large part of maybe one or both lungs such that if you were able to remove that particularly problematic area, you might improve the patient's elastic recoil, you might be able to improve their diaphragm movement, and maybe even hemodynamics, such that they're able to have better six-minute walk times and exercise capacity, and as a result, better quality of life.

Those are things that have come up out of the lung volume reduction surgery studies. But we're always looking for ways to do this in a less invasive way. So these endobronchial valves have gone through a few trials and will start to be used here with certain caveats.

So a variety of different types of bronchoscopic lung volume reduction have been tried in the past, including here. We were using the coils for a while. There are also some sealants, which is using biologic agents to be placed into areas of lung, things like fibrin, to induce atelectasis, essentially, of the areas of lung that are severely over-inflated.

But this new style is to put in these one-way valves into the areas of lung, again, that are severely hyper-inflated, as long as there's not collateral ventilation. So these valves were approved in July and will be coming to a pulmonary floor near you.

So important caveats to use of these valves is that when looking at CT scans of these patients, before they are permitted to proceed with these therapies, is that you have to have fissure completeness. And they are going to have to have complete treatments, such that there's not any further collateral ventilation of those areas of lung that are involved.

So in order to figure that out definitively, before they actually go to their therapy, is use of what's called the Chartis system, which is actually made by the same company as makes these valves. And what they do is it's a separate procedure where they undergo bronchoscopy. And the area of lung that's going to be targeted is occluded.

And then they measure flow and pressure to ensure that there's not collateral ventilation coming from other areas of the lung. For example, over here, on the left side of your screen, you'll see that, at this point, that area of the lung has been occluded. Flow completely drops off. So they can assume that area of lung doesn't have any collateral ventilation.

That's probably going to be a good candidate for these procedures versus some patients will have collateral ventilation and then putting a one way valve into that area is not going to do them any good. So three trials have come out in the last couple of years. I'll highlight this one, which is called liberate. It had 190 patients with two to one randomization.

So about double the number of patients got the valves versus what they called standard of care, which was just ongoing medical therapy. And so these patients had to have heterogeneous emphysema. You can't just have diffuse emphysema. You have to be able to target some area of the lung. And that was determined by looking at CT scans.

And then they underwent this Chartis procedure to confirm lack of collaterals. And they were able to reposition the valves later, if necessary. And what they looked at was the change in FEV1 greater than 15%. And they found that nearly 50% of the patients who underwent this valve placement were able to achieve that significant change in FEV1.

Other important outcomes that they highlighted was, again, a decrease in their St. George Respiratoy Questionnaire score. So improvement in quality of life, as evidenced by their reporting on this score. And six minute walk distances also were significantly improved after this valve placement. But then it's important to talk about what are the downsides of any new therapy.

And most notably, the biggest concern is of a significant rate of pneumothorax. As well as out of this group of patients, there were four deaths in the endobronchial valve group, three of which were attributed to early pneumothorax, and one that was attributed to late respiratory failure, probably unrelated to the procedure.

So looking at the three studies that came out, looking at this, they all confirmed the same general outcomes, which was improvement in lung function based on FEV1, increased exercise capacity, as measured by six minute walk distance, and quality of life, as measured by the St. George respiratory questionnaire. And so those are the three studies that support trialing these endobronchial valves in a wider population.

Now, in terms of safety, again, comparing to lung volume reduction surgery, we know that those patients oftentimes have early higher rates of mortality. And then if they make it out of the initial post-op period, then their life expectancy and mortality rate is improved. But when compared to the endobronchial valves, we see that there 90 day rate of mortality is lower.

Their rate of pneumothorax in lung volume reduction surgery is kind of part and parcel of the procedure. But it's important to keep in mind that this is still a significant number of pneumothoraces, especially for a less invasive procedure. So we know from looking at the Liberate Study, greater than 75% of the pneumothoraces occur within three days of bronchoscopy, which is also helping the group that is spearheading this to consider how long these patients should be monitored and in what setting in order to mitigate all of those safety issues.

In terms of other significant adverse events that are involved with endobronchial valve placement, other things to consider is the rate of COPD exacerbation. So we do see that endobronchial valve group, in the early days, had slightly more COPD exacerbation compared to standard of care. But over the longer term, the standard of care group probably had more COPD exacerbations.

That is, again, part of the reason that we would think about wanting to do this in a severe emphysema population would be to improve their outcomes on a variety of different levels, not only improved exercise, capacity, and quality of life, and FEV1, but also if there is a benefit in terms of COPD exacerbation. Then that would be useful to be aware of, as well.

So the selection criteria is not dissimilar from the selection criteria used for general lung volume reduction surgery. They have to have this heterogeneous emphysema. They need to have hyperinflation, as measured by looking at their TLC greater than 100% predicted. Their residual volume also needs to be very high.

I think for lung volume reduction surgery, it's generally greater than 150, in this case, 175% predicted. Their DLCO still needs to be greater than 20% predicted just to mitigate the severe outcomes in the sickest patients. And they need to have stopped smoking within at least four months. And they're excluding, primarily, patients who have more of like a bronchitic picture with a lot of sputum production.

So the program here is, I think, on the cusp of beginning. It's a multidisciplinary program, lots of people involved, everybody from radiology to thoracic surgery to our IP faculty, as well as our COPD faculty. And involvement of various different groups that will need to evaluate these patients for if they're appropriate for this procedure.

And remember, they'll have to go through two procedures. First, the procedure to ensure that there's not collateral ventilation, followed by the actual valve placement, followed by four night stay on our advanced lung disease service, in order to monitor them for that high risk of pneumothoraces, and management of that, if it does come up. So we will switch over to talking about critical care issues.

So I picked these two studies, as I mentioned, because a lot of the house staff have brought a couple of these up. So first, we'll talk about this smart study, which is looking at fluids and critical illness. So this was a study that came out of this question of what fluid is best to use in all these patients. So saline is the most commonly administered crystalloid worldwide.

And I think it's one of those things that it just gets started by the nurses, by the emergency department, by the floor. And it gets continued without a whole lot of thought that gets put into it. So the questions that have been raised in the past is, is are there any side effects from saline that we need to recognize? And should we be considering use of other fluids, as well?

Questions have been raised about the core hydrochloric metabolic acidosis that saline has been associated with, which has been shown to have the potential to decreased renal cortical blood flow through vasoconstriction, which could lead to increased need for renal replacement therapy, which you could extrapolate maybe might lead to a risk of increased mortality, which is how they came up with asking this question.

In some animal studies, it's been shown to have a decreased effect on hemodynamics as well as increased inflammatory cytokines. "But is this clinically relevant," is always the question. So this was a large study. Over 15,000 patients at Vanderbilt. And the way that this worked is they actually had a counterpart study, which was called SALT ED.

And what they did was for patients who were designated that they were going to go to an ICU, they randomized them to either saline or what they called a balanced crystalloid, which was either lactated Ringer's or Plasma-Lyte. The vast majority of them were lactated Ringer's. Only 5% of them actually ended up getting Plasma-Lyte.

But if they were designated to go to a certain ICU for that month, everybody would get whichever one of these fluids that they were randomized to. And that fluid got started in the ED and continued when they got to the ICU. This counterpart study, SALT ED, was for patients who were going to the floor. So similar idea. They'd get started on one of these two types of fluids in the ED and then sent to the floor.

And the fluids would be continued on the floor. That would line up with what they got in the ED. Note that the randomization was based on month. So if somebody was admitted, for example, at the end of a month, they may have been started on one type of fluid and then got crossed over to a new type of fluid. Because that's how the study protocol was written.

So there was a moderate amount of crossover. So some patients did get both types of fluid. So their primary outcome was a composite outcome, which always should give us a little bit of hesitation. Because how do we interpret this? But they called it MAKE 30, which was major adverse kidney events at 30 days, which included mortality, new renal replacement therapy, and persistent renal dysfunction, which they defined as greater than 200% of their baseline creatinine when they presented.

So what they found was for their primary outcome, this composite MAKE 30, they found that balanced crystalloids reached this outcome in 14.3% of the participants versus saline, which reached it in 15.4% of the participants. So we have to make what we will of this data. So the number needed to treat here is 91, based on this about 1% difference between these two fluids.

Interestingly, if you parse it down into these different components of what actually contributed to this composite outcome, the one that's contributing the most, although it itself was not statistically significant, was mortality, which is sort of unusual to expect that giving fluids would have an impact on, specifically, mortality, which is why that was not their primary outcome to begin with.

Of note, other things that they looked at-- secondary outcomes such as U-free days, ventilator-free days, vaspopressor free days, or worsening AKI. None of those had any difference between the two types of fluids. They did do a subgroup analysis of patients with sepsis. And they found that their in-hospital mortality had some difference, 25% versus 29%.

But again, it's a subgroup analysis. And if anything, that might just be hypothesis generating. So are smart things always better than not smart things? In this case, we could say maybe there's a trend favoring balanced solutions. In this case, lactated Ringer's more than even Plasma-Lyte, but it's probably modest. And there are a lot of limitations, here.

So this was an unblinded study. It was single center. Granted, it was a large number. There was crossover of patients depending on the month. And I think one of the things that makes this very difficult for me to think about applying to our patient population is they got a very modest volume of fluids. The median volume was about a liter.

Which if we think about the patients that come through our ED that we're really giving a significant amount of volume resuscitation to, almost invariably, they're going to get substantially more than a liter. So I'm not sure how this would play out in those patients. Again, there was a composite outcome. So a little bit hard to parse, because is mortality-- should that be valued the same as the other renal indices that they brought up?

And they had some caveats in their studies, such as their balanced solutions could have been held for hyperkalemia, which, from a physiologic standpoint, doesn't really hold up. Because things like lactated Ringer's and Plasma-Lyte do not need to be held in the case of hyperkalemia and have not been shown to exacerbate that. Of note, there's a slight cost difference between saline and lactated Ringer's, but maybe only about $0.25.

So I think one of the take-homes from this is to think about fluids like a drug, which I think we don't do as well as we probably should do. But there's probably no one right solution for every single patient, in the same way as we say there's not one right ventilator strategy for every single patient. It's probably worth thinking about, what's my patient at risk for? What's their acid base status?

Is there reason to use one fluid over the other? I think this and other studies that are looking at similar things with fluids maybe will help us better delineate who some of these fluids should be used in. There's currently a trial ongoing called the Plus Trial, which is looking specifically at Plasma-Lyte versus normal saline. And their primary outcome is 90 day mortality.

So we will see if there is any change there. And then lastly, vitamin C for septic shock. Here we are in the middle of the winter. So maybe we're all taking our vitamin C. So this study is interesting. It comes out of this recognition that vitamin deficiency is common in sepsis and septic shock and is associated with multi organ system failure and death.

But we don't really know anything about replenishment. You don't normally see us replenishing vitamins in the ICU. So this study came out of one single person's experience of giving three patients high dose vitamin C in the ICU-- three sick patients. After reading about this, he decided to give it to them. And apparently, they walked out of the ICU without any subsequent organ damage.

So the way that they designed this trial was it was a single center. They did it as a pre-post study. And they called it metabolic resuscitation for their patients with severe sepsis and septic shock. And they gave these doses-- vitamin C, 1.5 grams, IVQ 6 hours, hydrocortisone in a conventional dose, and thyamin 200Q, 12 hours, in combination with that vitamin C, in hopes of mitigating any risk of oxalate formation, which can be associated with vitamin C and lead to some downstream renal effects.

So their numbers were, granted, very small. So they looked at 47 consecutive patients with severe sepsis and septic shock that they gave this three drug regimen to. And then they compared it to historical patients. So this was not randomized or concurrent. But they looked at these historical patients that they tried to match with propensity scoring to compare severity of illness.

And they included patients with severe sepsis. They were measuring procalcetonin levels. And nearly half of each group had actual septic shock on pressors. So what they found, and the reason this generates all this buzz, is that in the treatment group, their in-hospital mortality was 8.5% versus 40% in the matched historical controls.

And they looked more specifically at duration of vasopressors, which was significantly less. 18 hours in the treatment group versus 55 hours in the matched historical controls. So this is very controversial. The way the study was done is controversial. The idea of vitamin replacement is very controversial. Some people may say, hey, it's a really relatively inexpensive therapy.

Look at what happened. We shouldn't be withholding this from people. And the other cohort of people may say, well, we don't really know what's working here and why. And it's a single center, a small sample size, very prone to bias. There was no randomization, blinding, concurrent controls. So I think there is a reason to have pause, but interesting to think about anyway.

I think there's a realization that there probably needs to be an RCT for those who believe that this concept may hold some water. And we know that we don't have great options for patients with severe septic shock. And for those that do survive, they often survive with severe sequelae, such as multi organ system failure and a lot of debility.

So if there is a hypothesis generation that comes out of this study, I think it may be able to add to the literature in that sense. So lastly, many of you know that my love is medical education. And there's been a lot of talk about wellness in academic medicine. So I was really moved by this piece that was in JGME, by one of our own faculty members in the internal medicine department at the VA, Gatin Scrow, who wrote this reflection piece about always feeling like we are trying to get to the next thing and putting life off in exchange for all the work that we do.

And he tells a story about how he was talking to a mentor of his. And his mentor told him there's no such thing as work-life balance. You need to give yourself permission to actually bring yourself to work, as opposed to keeping things completely separate. And so that really resonated with me. And so hopefully, thinking about all these wellness initiatives, as well as just progressing in our own learning, will grant ourselves and our trainees permission to bring ourselves to work, as opposed to only taking work home.

So this is my one-year-old with all this pulmonary pathophysiology booklet at home. And hopefully, we can work on finding more integration, rather than this elusive concept of balance. That's all I have.

[APPLAUSE]