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Immunosenescence and Inflammaging: Role of Aging as a Risk Factor for Severe COVID-19

Announcer:
Welcome to CME on ReachMD. This CME activity titled: Immunosenescence and Inflammaging, Role of Aging as a Risk Factor for Severe COVID 19, is brought to you by AKH, Incorporated, Advancing Knowledge in Healthcare, and the American Thoracic Society and is supported by an educational grant from GlaxoSmithKline. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Auwaerter:
Hello, and welcome to the program, Rapidly Changing COVID-19, The role of Monoclonal Antibodies. I'm Paul Auwaerter. I'm the Clinical Director for Infectious Diseases, and also the Sherrilyn and Ken Fisher Professor of Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland. I'm delighted that Dr. Tim Albertson is joining. Tim.

Dr. Albertson:
Hi, Paul. I'm Tim Albertson, Chair of Internal Medicine at the University of California Davis in Sacramento, and I'm a pulmonary critical care physician who has been working with COVID patients for now two and a half years.

Dr. Auwaerter:
Yeah, thanks, Tim. Certainly, the voice of experience in terms of dealing with the especially ill during the pandemic.

This part of the program is going to focus on immune senescence, but also explore another concept called inflammaging. And the idea here is to sort of review the role of aging as a risk factor for severe COVID-19. I think we're all familiar with the age gradient as perhaps the biggest risk factor for our patients for experiencing severe COVID-19.

So the learning objectives are three again, to explain immune senescence, the other is to examine the impact of inflammaging in COVID-19. And the last is to also assess the role of hyperinflammation in more severe disease.

Our agenda will include some general introduction of concepts regarding SARS-CoV-2 and ARDS, and explore sort of the dynamic spectrum that some patients experience with COVID-19 in terms of the pathophysiology, as well as age-related issues regarding to the immune response, and then we'll go through a summary as well.

Now, in terms of the SARS-CoV-2 virus itself, this is a virus that has turned out to be the most highly pathogenic of the coronaviruses. And of course, we've had experience with SARS-CoV-1, which honestly is probably more pathogenic on a mortality basis but wasn't as transmissible as this particular virus, and we'll explore that as well. They both belong to a group of lineage B coronaviruses that utilize the spike protein of the virus, and it harnesses to the ACE2 receptor, which is broadly present in many organs, especially the lung. And this is facilitates the entry along with a serine protease called TMPRSS2, which is important to allow cleavage of the spike to allow viral entry into the cell.

Overall, the infection progresses in many people with increased levels of inflammatory mediators. And of course, these end up being the way the body helps handle viral infections of this type. And after initial infection in the respiratory tract, or perhaps even in the gut, there's a variety of factors that have to do with the early so-called innate immune system, but also other components that organize

macrophages, neutrophils, and T cells.

Subsequently, especially if there is a good generation of an innate immune response and fast facilitation of neutralize using antibodies, there's often viral clearance with little in the way to show for anything in terms of severe infection. However, in certain patients, especially with the well-acknowledged now, risk factors for COVID-19, such as age, diabetes, heart failure, and morbid obesity and so on, all these seem to conspire to predispose the patient to experience hyperinflammation, which is a still a complex and not completely understood scenario. And this particular aspect may have to do with large amounts of virus present, as well as triggering certain immune factors such as high levels of interleukin-2, 10, also GM-CSF and others that trigger intense inflammation.

There are a number of risk factors, as we said, with the age gradient really the most important but certainly at least earlier in the pandemic, older men and men with comorbidities seemed to be more at risk than women. And especially troublesome were patients that really evolved into a picture that looked like there was significant lung injury and ARDS, often complicated by multiorgan system dysfunction.

And I wanted to ask Tim, you know, certainly we saw this earlier in the pandemic with the initial viruses that we saw in 2020, through the Delta, which is perhaps maybe the most pathogenic, but then certainly with Omicron, including the initial Omicron virus, but now even with subvariants, we haven't quite seen the toll. And of course, many people have already been infected and have acquired immunity or they've been immunized and boosted. Are you only seeing unimmunized people or people that have no history of COVID-19 in your unit? Or is it people that really just don't have great immune responses like solid organ transplant? Given the risk factors that we know, who are you seeing now that still lands in the ICU?

Dr. Albertson:
Yeah, only about a quarter of the patients admitted now even get close to the ICU. The vast majority are mild cases that are admitted for other reasons or asymptomatic. But those patients that are the sickest who come in with severe disease or moderate to severe disease, tend to be under-vaccinated or incompletely vaccinated. We do see a few breakthroughs, but the vast majority are not vaccinated or are immunosuppressed.

Dr. Auwaerter:
Yeah. So even if you have someone that's 85, but they may have some risk factors, but they're not immune suppressed. They've been immunized, for example, and perhaps boosted once or twice. You're not seeing those people in the ICU, it's only really if you think they don't have good immune response because of maybe medication or immune deficiency or so on.

Dr. Albertson:
Correct.

Dr. Auwaerter:
Yeah, yeah. So that's certainly an important concept, is certainly a large number of people remain unimmunized and especially may not have yet experienced any coronavirus infection in this regard.

The intense inflammation tends to cause other factors that could activate components within the endothelium that you might see consumption issues especially resulting in thrombocytopenia. Bone marrow often is suppressed because of inflammatory factors. And you will see lower white blood cell counts as well with lack of production and minor anemia, and also elevated liver function tests, especially in people that are more severely ill.

Imaging findings are interesting. And initially, there was very characteristic findings. In fact, before testing was developed in China, the CT was the method of diagnosing COVID at that time. If you had ground-glass infiltrates, as you see on the left, that was sufficient in the setting of, you know, high community rates of infection to secure a diagnosis. And indeed, many of our radiologists on CT would suggest COVID-19 as a diagnosis in the thick of the pandemic.

But, you know, when I'm talking with my radiologists now, they rarely see this. And of course, we're still getting a lot of CTs or CTAs to look for pulmonary emboli. And we're just seeing much less. And I'm interested, Tim, in your perspective on the West Coast, I'm an East Coast person. You know, of course, these variants tend to evolve differently in different areas, but that basically, we end up with the same. What's been your experience seeing the patients that, you know, that you're reviewing scans, perhaps on the floor rather than the ICU?

Dr. Albertson:
Yeah, we still see the ground-glass opacification. But more and more the ones who are actually making it to the ICU, and there's just not that many of them relative to the peak, have diffuse ARDS, or typical ARDS type findings. Not the patchy.

Dr. Auwaerter:

Yeah, not the patchy stuff that you might see before they hit that. Yeah.

And don't forget, of course, there's always secondary infections that patients may experience. Certainly, bacterial pneumonia. We saw much more fungal disease, I would say, complicating, certainly there much greater numbers in the hospital. So that's something we still consider, but perhaps not as commonly.

In terms of the pathophysiology, which this talk is focused on, one of the key aspects of coronaviruses are that it's a positive and single strand RNA. And RNA, that's single when - especially when it becomes double stranded, is part of its replicative nature in order to make more RNA, that double strand ends up activating danger signals in hosts subset. You have a generation of that early phase innate immune responses. So that's certainly very important.

And we've already talked about how the virus is a beta coronavirus. And there are larger numbers in the genera that also infect animals. In fact, it's such a widely distributed virus in animals, especially the beta coronaviruses in bats, certain warm-blooded mammals and so on, that, you know, hopes of eradicating this as we've seen the virus jump to animals, including dogs and deer and so on, I don't think there'll be much hopes of at all. People have given up on the concept of any eradication. There will likely be continued mutations, important points that we'll be discussing in other segments of this series.

Like any virus, the virus goes through a life cycle. Remember, viruses are not alive. We've all learned that medical school. They hijack host cells in order to make new viral components and make new virus. And almost all viruses enter by essentially co-opting normal post components and entering through what's a receptor but would be otherwise normal protein like ACE2, and then enters through endocytosis, or membrane fusion, and then hopefully makes its way into either the cytoplasm, or for DNA viruses, into the nucleus for replication.

In terms of making new proteins, there's both structural and nonstructural proteins, both need to be made by the host cell. They're then assembled and subsequently released.

This particular viral lifecycle is shown in this cartoon, where viruses will attach to ACE2 receptors, and then go through a fusion process, uncoat, and you can see the RNA as well as structural and nonstructural proteins being translated. Essentially important is a protease that is uncoated that will cleave a polyprotein. This is why nirmatrelvir, ritonavir, also known as Paxlovid, has its great impact here on preventing that polyprotein cleavage. This then goes through the Golgi apparatus where proteins are made, there's essentially assemble – assembly, budding, and subsequent release.

The coronaviruses have four structural proteins. I think everyone is familiar with the spike protein. The spike protein serves to facilitate attachment into host cells. And of course, this is where all the immune pressure is, why the virus continues to evolve and try to avoid existing neutralizing antibodies because they will bind to the spike protein. There's also membrane and envelope components, vital for forming the membrane structure, along with the nucleocapsid, which is important for helping to organize the RNA.

The spike protein is an interesting protein. It's a transmembrane protein, but is a trimeric glycoprotein. And virologists will talk about the protein actually moving into a up and down phase. And many of the changes to the spike protein cause the virus to be more in the down phase, which means it's less exposed or evades neutralizing antibodies. And so, we see this pretty repeatedly. And indeed, existing immunity, whether you've had acquired immunity from infection, or immunization with especially the mRNA vaccines, that immune pressure is such that is driving this RNA virus. And remember, RNA viruses have - their RNA polymerase is not quite as with the fidelity of DNA polymerases, so there's often introduction mutations, that essentially, most of them are rendered just a virus that's not able to be translated or productive, but just by sheer numbers of infection, of course, some actually end up being positive mutations, facilitating even more infection. And indeed, the spike protein itself, what's happened with each of these subsequent variants and subvariants are, it's become more transmissible because it ends up binding more tightly to ACE2 receptors. So it's actually able to enter more and more cells, and essentially cause productive infection. So that's why we're seeing as many infections as we do now. And of course, we're doing a lot of home testing, we don't - we're not really getting a true picture of the pandemic at the moment. And certainly, I think many of you know, family, friends, all of them, as the Omicron subvariants are evolving, that we're seeing more and more infections that people are not seeking hospitalization and so on.

So the ACE2 receptor we've already talked about as being very present in the lung, but it's also in the heart, one of the reasons why you might see myocarditis. Gut, certainly we see GI presentations. Less so with kidney and bladder issues unless if you're in that multi-inflammatory phase and severe illness.

So, one of the other things, which is very interesting of course has prompted a whole lot of speculation about the origin of SARS-CoV-2 is the so-called purine cleavage site, which seems to be unique among coronaviruses and has some hypotheses that this was introduced in a virology lab, rather than acquired through a natural means in animal populations. But this purine cleavage site is important and one of the reasons why this virus appears to be so well adapted to human infection.

Now, we're going to sort of segue into immune senescence and inflammaging, which is a central part of our talk today. And immune senescence, as it suggests, describes what happens in the immune system as we get older. And inflammaging talks about how a concept where as we get older, regardless of the excellence of our health, there is increasing amounts of low-grade inflammation that's often subclinical, it doesn't make you feel ill but will have impact on the immune system as well as organs.

So it's both of these concepts that are thought to contribute or arise even from conditions, that ended up being all the risk factors that we tend to see in severe COVID 19, not only the age gradient that we talked about, but many of the others for which you're familiar. And the other concept is, as we get older, especially as you head into the late 60s, 70s, and 80s, your both innate immune system and so called adaptive immune response, and that's the antibody-generating component, for example, as well as T cells, just are less nimble. They don't respond as fast and often have blunted responses. I mean, this is one of the reasons why we see influenza, even despite immunizations, more commonly in the elderly, and why a high-dose influenza vaccine is now recommended for that population over 65 in an effort to try to help stimulate more than standard vaccines, some increased responses in antibodies. And this also is why pneumonia is often called the Captain of Death, because it is more common in advanced ages. And so people not only have responded less well to vaccines, but of course, to infections of all kinds in that age range. So the risks seem to be over 60, although the CDC recently revised that over 50 as a potential risk factor, with greater morbidity and mortality, although again, this is a bit of a moving concept, as time goes on, in terms of whether the evolving variants change the rules in terms of risk factors.

Dr. Albertson:
Paul, can you comment on the pediatric multisystem failure patients and how they fit into the risk factor?

Dr. Auwaerter:
Yeah, so I think the pathophysiology for so-called MISC, the multisystem inflammatory syndrome in children, and the much less well understood and defined MISA a in adults, seems to be something that occurs after that initial 2- to 4-week illness. And people seem to have a rebound. You may not find virus. You can see antibodies to the nucleoprotein, or spike protein if they haven't been immunized, that would suggest they were infected or had an illness 2 to 4 weeks earlier. Often, it's not severe, but yet they behave as if they're in the middle of a hyperinflammatory syndrome. Not so much with ARDS initially, but initially, there's some confusion and overlap with Kawasaki's disease. Certainly, people have tried looking at IVIG. Also, corticosteroids in the MISC group, a lot of experience, especially in New York City. And, again, I think we're seeing less of this. I'm not a pediatrician. Certainly, it's come up when the numbers were much higher. And we've seen patients, adults represent 4 to 6 weeks after a diagnosis and we have not been able to find a secondary pneumonia, they don't respond to antibiotics, so on and so forth.

We've seen this, what's a little different here, Tim, at least my experience, of course, you know, you see it more in children. And we've seen it in younger adults. It's not necessarily an older adult situation, although we've also seen it in solid organ transplants, which makes me think that there may be some aspects where there's antigenic debris, some components of the viral genome that are still present that the host cell starts remanufacturing, triggering immune response. Of course, none of this, you know, is very clear. I don't know, Tim, what's your sense in – ?

Dr. Albertson:
Yeah, I think the same thing, but I'd have heard things like exosomes might be involved and other nontypical cellular components. Makes me wonder.

Dr. Auwaerter:
Yeah, certainly the whole exosomes concept is highly interesting, and how long they persist. You know, there's technologies now that are looking at exosomes as an easier way to make diagnosis early on, instead of antigen tests, being more precise and cheaper just because there's so much there's an abundance of exosomes in secretions and perhaps this is what's going on, you know, weeks later. So excellent question and thought there.

Now, I don't think anyone is surprised by data. At least, of course, this is mostly based on information from earlier phases, you know, certainly the first severe wave of Omicron going back to Delta, Alpha, and so on. But if you're taking children and adolescents and young adults as a reference group, as you move on in age, hospitalizations certainly are increased, and certainly death is as well. And deaths and over-65 group accounted for by far the most deaths in adults, regardless of other risk factors.

Now, with immunization, acquired immunity, decreased apparent pathogenicity of subvariants, and the latest subvariants, BA 4 and 5, which are now predominant as we're recording this in early July of 2022, don't seem to be any worse than they were compared to earlier Omicron subvariants. And that's also been the experience in South Africa, where BA 4 and BA 5 causes significant wave but without the severe COVID and hospitalizations seen in that earlier Omicron wave.

What of course blunts very much so, we know are primary immunization with boosters, especially in the older age groups, with the new

Omicron variants and subvariants, mainly because there's less protection. And we know immunity in terms of avoiding hospitalization in severe COVID-19 wanes after about 9 months after last immunization or boosting.

In terms of the effects on COVID-19, severe COVID-19, which typically is in that second week of illness, you know, it can be a little before 7 days, but on average, we start seeing problems around stay 6, 7, 8, 9. Early in the pandemic, average hospitalization day was often 8 or 9. Now I think people are more akin to coming to the hospital a little earlier when they're ill. But this is the phase where we see that hyperinflammation. And IL-6 was all the rage earlier, with measuring levels, I think we've moved away from that. But GM-CSF also has played central roles, at least in the earlier phases. And the thought is the immune senescence is one of the main risks along with the chronic subclinical inflammation from risk factors that drive severe disease in the elderly population.

Now, as we dive into the pathophysiology, this comes from a pattern recognition of regulators that the body is organized as a response to danger signals. And essentially, the lack of control often leads to higher viral levels. And what's interesting, and this may be with the subvariants evolving through Omicron, we see them binding more to the upper respiratory tract than the lower, is perhaps one reason why we're not seeing as much lung disease and hypoxemia in severe illness, despite the fact that people can feel very crummy. Certainly, I did as a 60-year-old early infection, but by day 6 and 7, I was feeling non-worse - non the worse and there's some thoughts and maybe because of less amount of virus in the lower respiratory tract. But the host itself distinguishes and finds unique molecular determinants based on locations. We've already talked about double-stranded RNA is one of the danger signals that triggers innate immunity.

This early immune response often is activated by Toll-like receptors triggered by RNA in endosomes. There's also a number of other factors listed on this slide, which are organized within the cytoplasm of the host virus that can recognize viral RNA, as well, and produce cellular damage in an effort to try to clear infection.

The immune response we've sort of chatted about, but in terms of what we see clinically and people, we'll see a high viral load often. You'll, you know, if you were to get cycle thresholds, the lower is more concerning. We'll will see cycle thresholds of only 12, 14, sometimes even lower in people completely immunized, and so on. Then we see high level of viral cycle thresholds in lower respiratory specimens. They'll be cytopenias, especially, with reduced natural killer in T cells. And then the elevated cytokines that drive much of the inflammatory responses in severe COVID disease.

Now, interferon production, especially gamma, beta, those that help control viral infection, are reduced as people age. And this is one of the other thoughts, and key factors, that there's less control with a viral infection; therefore, there's more virus and more tissues, and therefore more for the adaptive immune system to do; hence, the hyperinflammation.

This hyperinflammation, you know, the number of factors. You know, there's over 150, that have been described as being involved in this stage of the disease, along with mast cells, all in an effort that are thought to help recognize and clear viral products. And, you know, the thought initially is that you might help immune response downregulation by using tocilizumab, an anti-IL-6 receptor monoclonal antibody. But this proved to not be very helpful, whereas a very broad anti-inflammatory in the way of dexamethasone seemed to make all the difference early on.

And Tim, I'm just sort of interested just as we're talking about this pathogenesis in the ICU, were you someone that ended up using tocilizumab monotherapy early on? And have you now found that really, it's, you know, for those severe patients who we're using a broad, you know, dexamethasone but often adding on something like baricitinib to inhibit the JAK cascade, again, trying to downregulate immune responses? Or tocilizumab, in combination having an impact?

Dr. Albertson:
Yeah, we participated early on in the pandemic with Regeneron's IL-6 monoclonal antibody. And that study was stopped for futility. So I've never been that impressed. I looked at the inflammatory cascade as a spiderweb with all kinds of feed-forward feed-back systems in it and a lot of a genetic variability. Hard to predict when you start messing around with it. But we have not uniformly used it. Usually, we use bosutinib. Occasionally, we will use toc. But it is by far not a silver bullet.

Dr. Auwaerter:
Yeah, no, that's for sure. And you're using the combi - I mean, these are people already on dexamethasone, correct?

Dr. Albertson:
Absolutely. Absolutely.

Dr. Auwaerter:
Yeah. So in this hyperinflammatory phase, the thought is that there's excess cytokines and dysregulation that contributes to the severity. And of course, you know, I love Tim's analogy to a spiderweb in the sense that it is organized. I mean, spiderwebs are very

symmetrical, but there's a lot of components and sticky points and anywhere you hit the web, you might get stuck, but you know trying to get unstuck from that is not an easy pathway. And I'd have to say, although the drugs we just talked about certainly have a role and have lowered mortality and reduced length of stay and so on so forth, it's really the supportive care that medical care doctors offer that I think, including going to ECMO even and so on, that really have probably done as much as some of our medical intervention.

Tim, is that your sense that some of our better care - I remember early on, we tried to avoid intubating. We wanted to intubate patients early, and you know, that turned out not to be so good.

Dr. Albertson:
Yes, I think I think the sport of critical care is about just supportive care. And that anything we add on to that is relatively small compared to an organized supportive care approach.

Dr. Auwaerter:
Yeah, I couldn't agree more. And I'm speaking as an infectious disease consultant. there that, you know, we like to think our drugs that help viral infections make a difference. But it's really the supportive care and the host immune responses that makes such a difference.

So looking at immune responses to SARS-CoV-2, we've come to learn that, and this is not unique, certainly EBV and others have gone to ways of evading some of these early host responses efforts to try to corral the infection, such as really reducing the amount of type 1 interferon that's made. And this means that innate immunity really hasn't been engaged as much, and why immunization is so important, because that's what's giving you that head start in immune responses, even if it's not a perfect match, to help avoid the kind of large and widespread viral infections that help seemingly trigger, especially in older patients and others, this hyperinflammatory phase.

And as mentioned, the spike protein itself in SARS-CoV-2 has a great affinity for the ACE2 receptor. And indeed, the Omicron subvariants seem to have increasing infinity, although, again, there's also additional factors in terms of predilections, perhaps, where they actually appear most prevalent, although there have not been really exceptional studies delineating this with the latest subvariants. But this tight binding, it does seem to be the case and is one of the reasons why there's increased transmissibility of the latest subvariants.

This is quite a busy slide, but generally talks about what happens age wise. And of course, we all know infants are very susceptible to infection, because they haven't really had maturation of immune responses, they don't respond well to vaccines at early age, and so on. But as tolerance builds, as the thymus changes, and certainly as you hit puberty, there's fewer T cell responses. But generally, the effort of new or so-called naive T cells, decreases dramatically over time. So we build up sort of a production of cells that have had experiences, whether they're facing normal antigen and protein structures in our body that you don't want to react to unless you get autoimmune disease, or they're organized because of prior infections and so on. And also, there's a similar drop in a B cells. And all of these, including the peripheral and central lymph nodes, just generally are thought to be less responsive, and don't move quickly enough to sort of, you know, after an infection, they take a number of days to get activated and respond even if there's memory cells. So that's why the innate immune system is so important, and could be leading to some of the dysregulation that we see in terms of cytokine responses that would otherwise guide cells to places of infection and lead to viral clearance.

When T and B cells are responding to infection, as someone gets older though, they do not respond as well. Certainly, you're looking at adolescents and young adults, and this is some of the thoughts why you don't see much severe disease at that stage of life. And, you know, it depends also on the virus itself and its speed. I mean, influenza is something that moves quite rapidly. It's one of the reasons that it probably strikes elderly people more with severe illness, where you can have infection, and productive infection, and even symptoms in a matter of a couple of days.

The coronavirus seems to be slower, 3 to 5 days on average, which you would think affords more time for the innate immune system, but it's figured out more immune-evasive features such as decreased interferon responses, that really mean that you don't have - that extra time doesn't - hasn't bought people as much as you would hope. The lung damage from respiratory distress syndrome comes from this systemic inflammation.

And, Tim, I just wanted to ask you, I'm sure you know more about ARDS than I ever will, and you may have dealt with it on a far more of an occasion. Are there Are there features that you find especially unique driven by SARS-CoV-2 compared to other coronaviruses? Or is it just that here we have such a monomorphic illness in such high numbers? We're able to study one type specifically due to one condition and that's led to some of these therapeutic interventions that really hadn't panned out in the larger universe of ARDS.

Dr. Albertson:
Well, I think it's the latter. You know, we haven't had that many non COVID-related coronavirus ARDS cases. We had one 6 months before the outbreak. And it was a severe case of ARDS with coronavirus, not related to COVID. So I don't think that we have enough. I've always thought of coronavirus has been the summer cold kind of virus, that it was kind of low on the toxicity side. So I think we've

just seen a pandemic and we don't get to see pandemics very often. So we've had millions of cases to look at. And then I think we have a pretty good idea about this disease.

I did want to ask you though about to influenza and how we've changed our doses of vaccine for older patients with influenza. Is that part of this age-related immunosenescence process, where we see the similar thing with COVID vaccinations?

Dr. Auwaerter:
You know, it's interesting. Well, you know, whether higher doses would be called for in the COVID vaccines, you know, meaning you get more spike production, you know, and so on, it's an interesting one. Yes, to answer your question. Certainly, you know, the high-dose influenza vaccine, which will be likely recommended and preferred for people over 65, drives higher neutralizing antibody responses, and it does seem to enhance vaccine efficacy and reduce hospitalizations when it's been studied in the years that it's been studied.

Moderna, as its mRNA, does seem to generate more spike protein. But you know, the mRNA vaccines are interesting. I call them the Snapchat of vaccines because the RNA disappears rather quickly, the spike protein production doesn't last too much, which is one of the reasons I think boosting is so important to try to really make sure the immune system is seeing an amount of protein. So I've advocated, you know, we really need to adapt, you know what we did with RNA vaccines here to DNA, because DNA will last longer, you'll make more spike protein, and more robust immune responses. But I think that's going to be a nonstarter because no one wants their DNA changed. And it by injecting DNA, I think there's more concern along that line, which of course is not the issue with RNA vaccines.

So I think we've covered a very wide range of aspects with regards to how our bodies deal with the coronavirus infection and some of the foibles that come about as we get older or have significant comorbidities in combination. We don't really focus too much on the immunodeficient populations there, but obviously by impairing T and B cell responses, you just get much more latitude to the virus to make much more of it before there's some efforts at the body in terms of mounting responses.

So, again, in conclusion, immune senescence deals with the aging immune system and its impact. The thought about inflammaging is that some of those risk factors, diabetes, obesity, and so on, lead to chronic and low-grade inflammation that also advances with age, and is something where you will see elevated inflammatory markers as well. This hyperinflammation, whether you like the term cytokine storm, I think many people are pivoting to just hyperinflammation, rather than the storm, but does lead to severe immune responses and tissue damage, which of course, ARDS would be the Hallmark, but can be multiorgan system as well. Any immune response, especially in older adults is slower, less coordinated, and does make older adults more susceptible; all the more reason to try to be as proactive as possible, and give the body an advantage by providing boosting to existing responses with additional vaccine doses.

And lastly, the hyperinflammatory response definitely has contributed to more death, more hospitalizations, than the early direct viral cytotoxicity that the virus certainly can trigger some symptoms, but doesn't cause it severe illness that we see in that second week, as opposed to the first week of symptoms.

Tim, were there any other key points that you think you wanted to add as a takeaway from this presentation?

Dr. Albertson:
No, Paul, I think you've covered them all. And thank you for that excellent discussion.

Dr. Auwaerter:
Well, thanks, Tim for joining and providing some clinical perspectives as to why immune senescence is so important. I thank you for listening. And please join us in the other segments of this program regarding COVID-19, and the changing nature of the infection and therapeutic responses, as well as the role of monoclonal antibodies. Thanks so much for listening.

Announcer:
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