Medical Xpress

Q&A: Navigating cytokine storms

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It's a trajectory followed by many who experience a severe case of COVID-19: They feel poorly for a few days, improve over a day or two and then, a week or 10 days into their infection, have respiratory difficulties, a stroke, organ damage, or another dangerous complication and wind up in the intensive care unit.

While countless mysteries remain regarding this disease, some clinicians and scientists have come to believe that this resurgence of symptoms in certain patients is the outcome of a cytokine storm, an onslaught of immune activity that veers out of control, causing serious harm or even death.

With a mutual interest in immunology—both its helpful and harmful aspects—Nilam Mangalmurti, a physician-scientist at the Perelman School of Medicine (PSOM), and Christopher Hunter, an immunologist at the School of Veterinary Medicine, found they had a lot to discuss after colleagues introduced them two years ago. Their shared interest has gained a new relevance during the pandemic, and they recently teamed up to write a primer on cytokine storms for the journal *Immunity*.

Penn Today spoke with Mangalmurti and Hunter to discuss what they've learned, what questions are most pressing moving forward, and how emerging science is being applied to COVID-19 and other diseases.

How do you define cytokine storm and sepsis?

Hunter: The last time I had the flu, about 20 years ago, I had a fever, I felt like my bones were being crushed, and I thought I was going to die. That was not because the virus was replicating in my lungs and causing a huge amount of damage; it was that these soluble immune factors everywhere through my body—these cytokines—were causing this whole-body shutdown and making everything feel terrible. That's how people think about cytokine storms.

Everyone has cytokines circulating in their bodies; that's a normal part of the immune response. But when that response overshoots where it should be to clear an infection, that's where it becomes pathological and is considered a "storm." And it doesn't have to be an infection that triggers it. It could be that something turns on a T cell by mistake, it could be an

autoimmune response, or it could be a treatment that boosts the immune response to cure cancer.

Mangalmurti: Sepsis is now defined as an abnormal host response to a pathogen, whether it's bacteria, virus, parasite, or fungi. Most people should be able to clear the pathogen and return to a normal state. Sepsis is a dysregulated response where there is not necessarily a return to normal. In sepsis, the response is often characterized by both a hyperinflammatory and an immunosuppressive response happening at the same time.

Hunter: A cytokine storm can be part of that. The question is, At what point does cytokine activation become pathological? Immunologists may talk about cytokine storms, but I'm not sure we really understand why they make our muscles ache or cause a fever or respiratory distress or heart failure. That's one of the things we're trying to explain. Why does it feel like this? How does it amplify? Why do some people make an appropriate response to control infection and live while some overshoot and die?

A through-line of this work seems to be that the immune response isn't always either completely protective or completely harmful, but it can be somewhere in between?

Hunter: Yes, it's all about balance. Of course, we know that an immune response can be protective, but there are also immune-mediated diseases. Everyone knows someone with an immune-mediated condition like arthritis, lupus, diabetes, and inflammatory bowel disease.

How have the two of you been working together?

Hunter: When Nilam and I first met I quickly realized my interests coincided with hers. I do basic immunology studying mice, while Nilam's science is informed by her time in the ICU. I've enjoyed getting her perspective on how disease works and the model infectious system that my laboratory uses. When *Immunity* asked us to write a primer for people who didn't really know what a cytokine storm was, we took that opportunity and ran with it.

Mangalmurti: A pandemic is never a good thing, but it has been a learning opportunity for all of us and a chance to bring together bench-based scientists with physicians and physician-scientists. We have a huge number of sepsis researchers on campus that don't necessary think they're studying sepsis or don't contextualize their work that way.

A group of physicians and immunologists, including Chris and myself, started a joint sepsis working group so we could bring together scientists from many walks of life, so anyone from clinical epidemiology to fundamental basic scientists. The first meeting we had there were so many ideas flying back and forth about sepsis and pathogens and host response. It was exciting to see people from PSOM, the Children's Hospital of Philadelphia, and Penn Vet so engaged.

Now with the pandemic, a focus on understanding the host response to infection is amplified and relevant to questions like why some people with COVID have no symptoms while others get hit really hard.

How is what we're seeing with COVID-19 confirming or changing what we understand about cytokine storms and how to address them in patients?

Mangalmurti: Part of why I wanted to do this primer was to sort through this amazing amount of information about COVID that has been pouring

in from Twitter, bioRxiv, and medRxiv and other places and try to make sense of it.

There was an opinion piece in the Lancet early on in the pandemic that everyone latched onto that suggested that specific therapies to tamp down cytokine storms were going to be beneficial for COVID. It was early in the pandemic, and this idea seemed to make sense. But we don't have rigorous evidence to back that up and, as we have learned more, we realized that it is not so simple.

In sepsis, multiple therapies to block cytokine have been tried before, and there hasn't been any survival benefit. In fact, there has been some increased mortality, maybe because the drugs are not striking the right balance of immune response versus immune suppression or are not being used at the right time point in the infection.

One thing that was very clear to us after the first week of seeing COVID-19 patients was that most who came into the ICU with organ failure clearly had a condition that seemed to predispose them to vascular injury: obesity, diabetes, high blood pressure, age, a history of vascular disease, or clots. And that was striking because it's not something we usually see in most other forms of sepsis, or other forms of acute respiratory distress syndrome.

That got us thinking about innate immunity in the vascular compartment and whether this virus had a penchant for the vasculature. Maybe there's a way to use what we know about this relationship with the vasculature to design and use more targeted anticytokine therapies.

Of course, when patients are doing poorly, clinicians are often desperate for a treatment. I understand that; we just need to remember to proceed with caution when we're treating with drugs outside of a controlled trial.

Hunter: From my perspective it's exciting to think about targeted therapies that are already available, like antibodies to cytokines that are already used in the clinic; maybe they could be repurposed and used in this setting. But we really need large clinical trials to assess whether our excitement about some of these approaches is meaningful and valid. Perhaps one consequence of the pandemic is that more people will be thinking about how to more effectively use cytokine therapies or cytokine neutralizing approaches, not just in COVID-19 but in sepsis in general. Sepsis is a disease where the advances in immunology have not yet had the same impact that they have in other conditions, such as cancer and autoimmunity.

Can the idea of a cytokine storm help explain the spectrum of responses we've seen to the coronavirus, from asymptomatic patients to those with severe disease?

Mangalmurti: There are certainly anecdotes from people who get this disease that they are home, they're having fevers every night, they don't feel well. These people are having a cytokine storm, but it resolves, and they don't end up on a ventilator in the ICU. Maybe those patients don't have the predisposing factors that we talked about. It could also be that they have less of a viral load.

Hunter: No one is studying the asymptomatic patients. One question is, How asymptomatic are they really? Maybe they had a small fever one day; maybe that was their cytokine 'shower." Also, as Nilam mentioned, in every other system the amount of the virus you are exposed to matters, so I'm not sure why it wouldn't matter here, too.

You wrote this primer hoping to reach an audience of

immunologists. What do you hope they start doing or doing more of?

Hunter: We, the basic immunologists, need to be thinking more about the physiology of what we're doing. Often, we'll look at immune cells in isolation. We need to look at their effects on the vascular system, the impact on lung function, the impact on heart function. In general, we need to realize that it is really important to understand a whole disease process, to look at the system more broadly.

Your work seems to underscore the value of collaboration across fields.

Hunter: Absolutely. Nilam has worked on sepsis and has been seeing sepsis patients for a long time. She's dealing with really sick patients who have a lot going on. Basic scientists tend to want to simplify and reduce things. And you've got to meet somewhere in the middle, I think, for complex diseases. Penn is a really good place to do that, at PSOM, CHOP, and Penn Vet.

Mangalmurti: I'm usually talking with clinicians about ARDS and sepsis, and now to partner with immunologists who are taking a deep dive into the cytokines, into the pathobiology of these things and looking more at the host-pathogen interface, it's a really nice intersection. As awful as the pandemic has been, I hope some of our trainees will be intrigued by all these unanswered questions and want to learn more about disease processes.

More information: Nilam Mangalmurti et al., Cytokine Storms: Understanding COVID-19. *Immunity* (2020). DOI: 10.1016/j.immuni.2020.06.017

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