Ask Your Friends: Locally Sourcing During Covid-19 Crisis

Chapter 4: Five Blind Men and an Elephant

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Experts agree there is a coagulation problem with COVID-19; yet, standard anti-coagulation protocols do not seem effective. Patients on low molecular weight heparin (LMWH) get transferred to the ICU. Subsequent doubling of the dose in the ICU does not prevent the findings of thrombi in organs at autopsy. COVID-19 affects many different organs in the body.

Let’s have a conversation about a possible link between the coagulation system and disease manifestations in a variety of organs, through the eyes of frontline physicians, friends and family of mine, who are all treating patients with this disease.

Last weekend I sat down with Madeline Fitzpatrick, MD, an intern in Internal Medicine at the University of Tennessee in Nashville, to discuss her findings surrounding the COVID-19 outbreak. I visited Madeline and my son, Jack, as it was their first wedding anniversary.

“What is the most common problem that you see in your COVID-19 patients?” I asked.
“COVID pneumonia,” she said.
“What kind of symptoms do these patients have?”
“Cough and shortness of breath. To qualify for admission to the hospital, COVID-19 patients usually have a low oxygen (O2) level, which is detected by an O2 saturation machine.”

“What do you think may be causing this low oxygen level?”
“It is very clear that low oxygen levels in pneumonia are due to what is called V/Q mismatching. This is a condition in which one or more areas of the lung receive oxygen but no blood flow, or they receive blood flow but no oxygen (O2) due to some diseases,” according to Dr. Madeline Fitzpatrick. “V refers to ventilation; Q refers to blood in the lungs. V brings O2 into the lungs. The Q carries the O2 out. In bacterial pneumonia, for example pneumococcal infection, most of the problem is in the airways due to pus filling the air sacs (alveoli) – the V side of this equation. In COVID pneumonia, most of the problem is due to the “Q side” of the equation, the blood. This blood flow problem could be caused by microthrombi (small clots) in the lung.”

When I returned to Hattiesburg, I had a conversation with Steven Stogner, MD, the Director of Critical Care at Forrest General Hospital (FGH) and a Pulmonologist at Hattiesburg Clinic (HC).

“Dr. Stogner, you have more experience. Do you agree with Dr. Madeline Fitzpatrick?”

“COVID-19 causes COVID pneumonia in the lungs, so I agree that this could be explained by microthrombi or small clots in the lungs,” Stogner said.
Stogner then asked me as a board-certified nephrologist, “Dr. Fitzpatrick, how does COVID-19 affect the kidneys?”

“Patients with COVID-19 can get acute kidney injury (AKI), often severe enough to require dialysis,” I said. “Microthrombi or small clots in the blood vessels in the kidneys could be a factor in AKI. However, it is not the only factor. Volume depletion, red cell stacking, direct tubular injury by virus or hypotension are other mechanisms contributing to AKI in COVID-19. Furthermore, COVID-19 patients on dialysis tend to clot the dialyzers, which could also be due to microthrombi or small clots in the dialysis circuit.”

Ashli Fitzpatrick, MD, an intern in Internal Medicine at Massachusetts General Hospital (MGH), who is about to start her Dermatology residency at Vanderbilt University Medical Center, joined in on the conversation in Nashville via FaceTime.

“How many COVID-19 patients are in the hospital at MGH?” I asked.
“Currently, there are 350,” Dr. Ashli Fitzpatrick said.
“What are the dermatologists at MGH seeing in their patients with COVID-19?”
“COVID toes. This could be caused by microthrombi in the toes,” she responded.

Esther Freeman, MD, the Director of MGH Global Health Dermatology and a member of the American Academy of Dermatology task force on COVID-19, was quoted in USA Today last month, stating, “It is possible COVID toes could be caused by small blood clots that form inside the blood vessel.” Dr. Freeman said other mechanisms could also be involved.

Jack Fitzpatrick, MD, an intern in ophthalmology at Vanderbilt University Medical Center (VUMC) in Nashville, TN, said he saw a COVID-19 patient with third nerve palsy in the ER at VUMC that weekend.

“There was no alternative explanation for this, other than a remote history of Lyme disease,” he said. “It could be due to microthrombi, small clots to the vessel supplying the third nerve. The third nerve palsy was complete and painless, more suggestive of a vascular cause. The MRI showed scattered T2-FLAIR hyperintensities likely reflective or microvascular change.

Roberto Pineda, MD, an Associate Professor of Ophthalmology at Massachusetts Eye and Ear Infirmary (MEEI), agreed.

“We just saw two COVID-19 positive cases this weekend in the emergency room at MEEI with fourth cranial nerve palsy,” Pineda said. “As may be the case with Dr. Fitzpatrick’s case in the ER at VUMC, I believe these findings could be explained by microthrombi.”

I spoke with Karla Perrizo, MD, a Yale-trained, board-certified anatomic pathologist at UMMC in Jackson, MS. I asked if she could review the autopsy findings in patients who have died from COVID-19 complications.

She responded, “The literature shows the presence of microthrombi (small clots) in the lungs and the kidneys.”
“So these findings would support what the specialists above are speculating may be causing the symptoms in their patients?” I asked.
“Yes. Absolutely,” she replied.
I then turned to my colleague, Bryan Batson, MD, the Chief Medical Information Officer and clinical lead of COVID-19 response at HC, who is board-certified in Internal Medicine and Hypertension, and asked, “What are the risk factors for getting sick from COVID-19?”

“Age over 40, BMI > 30, hypertension, diabetes mellitus, chronic kidney disease, and CHF,” he said. “In my studies of the first 12 patients admitted with COVID-19 from HC, 8/12 had recently been treated with steroids.”

“Dr. Batson, what do these conditions have in common?”
“They all have elevated levels of Plasminogen Activator Inhibitor, PAI-1,” he said.

What is PAI-1?

PAI-1 is the opposite of tissue plasminogen activator (tPA). TPA is used to treat clots, for example, strokes, heart attacks, and pulmonary emboli. TPA breaks down clots, and patients with elevated levels of PAI-1 have increased risk of clots.

The coagulation system is a delicate balance between the tendency to form clots to stop bleeding, and the breakdown of clots (fibrinolysis) to prevent clots from enlarging. In the coagulation system, the conversion of Plasminogen to Plasmin is mediated by tPA. Plasmin degrades fibrin in intravascular thrombi. PAI-1 inhibits tPA. At HC, we believe that PAI-1 could be a unifying explanation to clarify why patients with COVID-19 develop clots in multiple organs.

“Dr. Batson, if tPA dissolves clots, can it be used to treat patients with COVID-19?” I asked.
“Yes. TPA has been used in patients with COVID-19 with positive results.”

Interestingly, the nephrologists at HC noticed in mid-March that dialysis catheters flushed with tPA ran continuously for days. More recently, there have been reports published about using tPA successfully in COVID-19 positive patients.

“Is that the answer then? Give all the patients tPA?”
“I would caution against that, especially in patients who are less sick,” Batson said. “TPA is a very powerful blood thinner and could have a significant risk of bleeding. There have been reports of bleeding in COVID-19 patients given tPA. Also, tPA needs to be given by injection intravenously, and given that microthrombi are one of the earlier disease manifestations, it would not be easy to administer safely.”

“Are there any other options?”
“Quite possibly. It’s called Natto.”
What is Natto?

I called and asked Jennifer Lemacks, PhD, RD, LD, a Nutrition and Disease Professor at The University of Southern Mississippi (USM), to answer that question. She explained that Natto is a food that is usually eaten for breakfast in eastern Japan. Natto is soybeans, fermented with bacillus subtilis, and is typically served in 3.2oz portions. It is readily available at many Asian food markets, such as the B&K Seafood and Asian Food Market in Hattiesburg.

“Dr. Lemacks, how might Natto help with microthrombi (small clots) which, per the doctors above, may explain many of COVID-19 disease manifestations?”

“3.2oz of Natto contains 90-100mg of a potent fibrinolytic enzyme called Natto Kinase (NK),” she said. “NK has three modes of action that can help break down clots. NK degrades fibrin directly, converts pro-urokinase to urokinase (also breaks down clots), and increases tPA formation.”

“Is there any evidence that Natto is safe to use?” I asked.

“Yes. Of the human studies done, NK supplementation has been used daily in patients over at least eight weeks with no known side effects,” according to Lemacks. Based on the available evidence, I would expect natto as a food source of NK to be safe as well.

“Dr. Fitzpatrick, is there any evidence that Natto affects the coagulation system in any patients that you have treated with COVID-19?”

“Yes. I treated one of my patients with Natto. My patient’s d-dimer levels rose by 50% six hours after eating it. This is consistent with published effect of Natto on d-dimer levels.”

“What is d-dimer, and what has it got to do with clotting?”

“D-dimer is elevated in patients with clots. It rises in the blood when the body is attempting to break down clots using its own clot breakdown system called the fibrinolytic system. The higher the clot burden in the body, the higher the d-dimer level.”

(Pictured: Yan from B&K Seafood and Asian Food Market in Hattiesburg, MS)
“Are d-dimer levels elevated in COVID-19 if clots seem to be the problem?”
“Yes,” I responded. “According to a recent New England Journal of Medicine publication, D-dimer levels are elevated 46.4% of patients with COVID-19. In fact, the higher the level, the worse the prognosis.” (NEJM, 2020)

I believe that coagulation abnormalities in COVID-19 need further study and similar to the country’s approach with vaccine development. Perhaps, it would be reasonable to consider exploring research into many different components of the coagulation system.

Dr. Pineda said this reminded him of the parable of *The Blind Men and an Elephant*. *The Blind Men and an Elephant* is a famous Indian fable about a group of blind men who encounter an elephant for the first time. They go up to the elephant and begin touching it. They each feel a different part of the elephant’s body, but only one part, like the side or the tusk, so they all have different descriptions of what an elephant looks and feels like.

The moral of the story is that humans tend to believe only what they see in front of them. They claim absolute truth based on their own limited, subjective experience and ignore others, because it’s hard to see from another person’s point of view unless you are standing in their shoes.

“Dr. Fitzpatrick, do you believe that PAI-1 explains all the findings in COVID-19 related illness?”
“Absolutely not,” I said. “There are several features of the disease that cannot be explained by this alone.”

We have not been able to explain the increased incidence of macrothrombi such as DVT, pulmonary emboli, acute stroke, acute myocardial infarction, or renal artery thrombosis by this mechanism. Microthrombi, induced by PAI-1, could be involved in injury to the lungs, kidneys, skin, and eyes as suggested above. Microthrombi may also be involved in the brain, causing confusion, heart, causing reduced pump function, and possibly other organs. Per the literature, other factors may be involved. For example, anti-phospholipid antibodies could be the additional factors contributing to hypercoagulability.

Another component of Virchow’s triad, vascular injury, could also be a factor. Our current thinking is that vascular injury, specifically endothelial injury, may come into play later in the disease process. There are other pathological features in autopsy studies that are not explained by
microthrombi alone; for example, red cell aggregation in small vessels are noted in autopsy specimens in lungs and kidneys. These red cell aggregates, sometimes described as “rouleaux” or “cattle trucking,” could be a different mechanism resulting in ischemic injury in the kidney. Direct tubular injury by the virus itself and septic shock are other factors causing AKI.

Dr. Perrizo mentioned that there is a report of involvement of the terminal complement components of the complement system in lung and skin lesions, suggesting systemic activation of the alternative and lectin-based complement pathways.

There are components of the disease that may be due to the direct effects of the virus itself: effects due to viral binding receptors, effects due to release of substances from infected cells, effects due to crenation of cells as the virus robs membrane components, effects on the immune system, the coagulation system, the red cell system, the renin-angiotensin system, the complement system, the cardiovascular system, and the inflammatory cascade. Clearly, this COVID-19 disease is very complex, and it is likely that there are many pieces to this puzzle. This is probably why it has not been solved yet. Perhaps we need more than five blind men feeling this elephant.

“Dr. Batson, as the clinical lead of the COVID-19 response team at HC, have you changed the management of patients based on this information relating to microthrombi,” I asked.

“Yes. First of all, we recommend that all of our COVID-19 positive patients exercise, as simple as walking two miles per day,” he said. “Exercise reduces stasis, one of the factors that Virchow identified that predisposes to clots.” He added, “Of course, we recommend that our patients wear a mask while walking and practice six feet of social distancing.”

Batson continued, “Exercise also boosts the immune system. It lowers PAI-1 levels which should reduce clotting tendency, the second factor described by Virchow that contributes to clotting,” he said. “For patients over 40, or under 40 if they have risk factors, we have added Natto 3.2 oz daily for 15 days in our COVID-19 patients, as long as they are not on Warfarin or DOACS.”

The advantage of Natto is that it is inexpensive. It is less than four dollars and it’s readily available. My children made Natto in my home as part of a COVID-related, science experiment. A local Asian market is giving coupon discounts to our patients. Some patients find it a little bland, but we have suggestions to make it more palatable.

Dr. Lemacks pointed out earlier that Natto has been given safely to patients daily for eight weeks with no side effects, so I have absolutely no problem giving Natto to our patients. As Hippocrates stated, “I will use those dietary regimens which will benefit my patients according to my greatest ability and judgment, and I will do no harm or injustice to them.”

“Do you believe that Natto may have benefits beyond COVID-19,” Dr. Batson asked.

“Yes, I do. I believe that PAI-1 may have broader implications. PAI-1 may be a key factor in long term cardiovascular risk, which is the number one killer in the U.S., Mississippians being close to the top of that list. Exercise and diet high in fruit and vegetables also lower PAI-1.”
In the Ibaraki Prefecture, the center of Natto production in Japan, they eat Natto regularly, and the incidence of cardiovascular disease is amongst the lowest in the world.

Medications used to lower CV risk such as ACE inhibitors, statins, and SGLT-2 inhibitors all lower PAI-1 levels. In patients who can’t exercise, or those who have limited access to fresh food and vegetables and many times can’t afford these expensive medications, perhaps Natto could help lower their CV risk. Natto would also be a less expensive option for patients who have no or inadequate insurance coverage.

**Can this be studied to see if this is true?**
Absolutely. We would love to get research funding to study this in Southern Mississippi. We are fortunate to have outstanding research labs at USM, led by Dr. Mohamed Elasri, Director of the Mississippi INBRE network. Within days of the COVID pandemic arriving at our doorstep, Dr. Elasri’s lab helped us get COVID-19 testing up and running for our patients.

At HC (per HIMSS), we have the best infrastructure in the U.S. to do population health. Using our population health infrastructure to manage our Medicare ACO with almost 20,000 patients, HC was the number one ACO in the U.S. in quality in 2016 and 2017. In 2018, we saved Medicare 9.2 million dollars. Mississippi has the highest prevalence of cardiovascular risk factors, hypertension, diabetes mellitus, and chronic kidney disease in the U.S.

I am a Nephrologist. I moved here from Boston because there are so many patients with end-stage renal disease (ESRD). Much of this ESRD can be prevented with the right approach. I believe research funding should flow where it is most likely to have a translational effect of the population. Because if this, HC and USM have assembled a transdisciplinary team of nutritionists, behavioral therapists, and a physician with an expertise in “food as medicine” to work with our existing population health management team. We hope to expand these efforts with new sources of funding.

If the NIH was to fund initiatives at USM and HC, I am highly confident that we could transform the health of the sickest state in the nation. We would use the funds to scale innovative approaches to the African-American community, in particular, to reduce health disparities in the area.

The COVID-19 crisis has already created a meaningful dialogue between HC and the African-American community, which was facilitated by Dr. Elasri from USM. We would use a portion of the funds to expand mental health (which is currently inadequate in our population health strategies), and we would use some of the funds to expand innovative, population health strategies we already have in place at HC that could be shared with the rest of the country.

USM has the infrastructure in place to do the basic science research and has already received funding from NIH to reach out to African-American communities with strategies to transform eating habits. However, these efforts, which have shown early success, need to be scaled drastically. Currently, only 20 patients are enrolled in this program.
HC is already sharing our population health strategy with the University of Mississippi Medical Center, in Jackson, MS. Batson and Daniel McCall, MD, (McCall is the Director of population health at HC) have been nationally recognized for HC efforts in the area of population health. HC’s ability to partner with USM during the COVID-19 crisis has received national attention. Our efforts were featured in two leading articles on the American Medical Associations’s website. We also received recognition in an article published by the NEJM Catalyst.

I asked myself this question: **What is it like to have so many family members on the front line facing this pandemic?**

My wife, Nancy Perrizo, MD, an internist, and I live in fear every day that one of our friends or family may get this disease. Our anxiety was heightened by the media reports of shortage of PPE in hot zones, prompting us to mail PPE to our daughter in Boston as a back-up.

Being a health care worker should be added to the list of risk factors due to repeated exposures. I suspect the poorer outcome in health care workers may be due to higher viral load as a consequence of repeated exposures. My wife’s nephew, Darin, who lives in Minnesota, already contracted COVID pneumonia and got very sick from the disease but ultimately recovered. My best friend, Frank, who is an Anesthesiologist in Dublin, also got infected. Thankfully, he is doing well.

This is a disease the world has never seen before. The novelty of this virus is contributing to the chaos. We have been doing the best we can in Hattiesburg, mostly using local resources to fight this pandemic. Our hope is that federal funding that has been allocated to this effort will flow to the front line and not get clogged in regional corridors of power. It would be a tremendous blow to Hattiesburg if we could not continue and expand testing locally for our community.

I reached out to a friend of mine, Steven B. Deitelsweig, MD, the Vice President of Medical Affairs at Ochsner Health in New Orleans, LA and Associate Professor at Tulane University School of Medicine, to get his expert opinion on coagulation abnormalities.

“**Dr. Deitelzweig, you a leading expert in coagulation abnormalities. What are your thoughts on coagulation abnormalities in COVID-19?**”

“I have been very impressed with this active discussion and associated thought-provoking hypothesis about what is being seen globally as a very high incidence of thromboembolic complications, especially venous thromboembolic (VTE) complications, in hospitalized COVID-19 patients, Deitelzweig said. “COVID-19 patients have been noted to have significantly elevated markers of hypercoagulability including d-dimer (Dd), fibrinogen levels, FVIII levels, short activated partial thromboplastin time (aPTT) and Sepsis-Induced Coagulopathy (SIC) scores with an increase in venous thromboembolic disease as well as cardiac injury, for which potential causes may include atherothrombosis, demand ischemia or micro-thrombosis. The mechanism underlying morbidity related to thrombosis in COVID-19 patients remains unclear. I did see some remarks about an elevated D-dimer is expected with severe COVID-19 which I would offer that currently that is being viewed as a marker of poor prognosis.”
This development seems most notable in our sick hospitalized patients in Intensive Care Units with respiratory failure. Although hospital and antithrombotic guidelines advocate for routine VTE risk assessment and use of standard thromboprophylaxis, recent reports also suggest the failure to prevent thromboembolic events in these patients using standard or routine thromboprophylaxis strategies, likely due to the prothrombotic state seen in these patients. To date, there is only data from observational studies from the Wuhan, Netherlands, and other centers reports to inform the optimal dose of heparin thromboprophylaxis in the sick, hospitalized, and likely prothrombotic COVID-19 population. Many of us from multiple international antithrombotic societies have advocated high quality data from a randomized trial to inform this critical clinical question, and to definitively answer the question of whether empiric treatment dose heparin therapy confers a net clinical benefit to reduce major thromboembolic events and associated mortality in this population.

At present and mostly based on expert opinion, my recommendations are as follows:

A) For all non-critically ill patients (i.e., not in an ICU) with confirmed or highly suspected COVID-19, we recommend standard dose VTE prophylaxis as per existing societal guidelines for medically ill and surgical hospitalized patients. Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols.

B) For critically ill patients (i.e., in an ICU) with confirmed or highly-suspected COVID-19, we suggest increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous three times daily, or low-intensity heparin infusion). Dose adjustments for renal function or extremes of weight should follow product labeling and/or institutional protocols. Individual hospitals should determine which regimens best align with their institution’s experience and workflow. I also hope that insurers in Mississippi will agree to payment parity for tele-visits, following the lead of Medicare and private insurers in Louisiana.

Given the very dynamic nature of this pandemic, it is essential to apply rational evidence-based approaches whenever possible, stay apprised of emerging evidence and modify practice accordingly. I believe that coagulation abnormalities in COVID-19 warrant further study and similar to the country’s approach with vaccine development, perhaps it would be reasonable to consider exploring research into many different components of the coagulation system.
Family:
Madeline Fitzpatrick MD (Daughter in law)
Ashli Fitzpatrick MD (Daughter)
Jack Fitzpatrick MD (Son)
John Fitzpatrick MD (Me)
Karla Perrizo MD, (Daughter)
Nancy Perrizo MD (my wife)
Joe Campbell MD (Madeline’s father)

Friends:
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Steven B. Deitelsweig MD, Vice President of Medical Affairs Ochsner Health, New Orleans, LA, Associate Professor at Tulane University School of Medicine.

References: