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## Predicting Outcomes in Older Medical ICU Survivors

Adults over the age of 65 now comprise almost half of all intensive care unit admissions in the United States. Receiving more intensive treatment than in years past, they often survive what were previously fatal critical illnesses. However, among the some 125,000 older adults who require mechanical ventilation and survive to hospital discharge annually in the country, almost half are re-hospitalized and 30 to 65 percent die within six months.

"These data demonstrate an urgent need to risk stratify and identify older ICU survivors for interventions aimed at improving their functional dependency, mortality, and/or quality of life after they are discharged," says **Matthew R. Baldwin, MD, MS**, pulmonologist on the Critical Care Service in the Division of Pulmonary, Allergy, and Critical Care Medicine at NewYork-Presbyterian/Columbia University Medical Center. Dr. Baldwin recently served as lead investigator on a study to determine whether frailty can be measured within four days prior to hospital discharge in older ICU survivors of respiratory failure and



Dr. Matthew R. Baldwin

whether it is associated with post-discharge disability and mortality. This study was funded by a new investigator pilot award from the National Institute on Aging and the Weill Cornell-based Translational Research Institute for Pain in Later Life (TRIPLL).

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## Bench to Bedside and Back to the Bench: Collaboration in the Medical ICU

When **Katherine A. Hajjar, MD**, Professor of Pediatrics, Brine Family Professor of Cell and Developmental Biology, and Associate Dean for Research at Weill Cornell Medical College, came to Weill Cornell Medical College as a young assistant professor in 1984, she began working on endothelial cells in culture with **Ralph L. Nachman, MD**, who at the time was Director of the Specialized Center of Research in Thrombosis and Chief of the Division of Hematology-Oncology in the Department of Medicine.

"We discovered over those first few years that there was a protein on the surface of endothelial cells that stimulated the fibrinolytic system – the system that breaks down blood clots," recalls Dr. Hajjar. "Over the next several years, I worked

with others in my lab – some very talented young scientists – to understand how this system worked at the molecular level." Dr. Hajjar's laboratory demonstrated that annexin A2 (A2) regulates hemostasis in humans through studies in patients with acute promyelocytic leukemia in which overexpression of A2 correlates with severe, sometimes life-threatening hemorrhage. The research team also determined that individuals with antiphospholipid syndrome often have thrombosis in association with high-titer anti-A2 antibodies that inhibit A2 function or activate endothelial cells.

After identifying the annexin A2 protein as a key component of the fibrinolytic system, the next major step for Dr. Hajjar and her team was to move

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## Predicting Outcomes in Older Medical ICU Survivors (continued from page 1)

Frailty as a syndrome has been defined by **Linda P. Fried, MD, MPH**, Senior Vice President of Columbia University Medical Center and Dean of Columbia University Mailman School of Public Health. In her research in a community dwelling population, Dr. Fried found that frailty is a predictor of adverse outcomes. This construct has been applied to patients in the hospital, but it had not been tested in the ICU setting.

“Physical frailty is a measurable clinical phenotype of increased vulnerability for developing adverse outcomes, such as disability and/or mortality, when exposed to a stressor,” explains **Thuy-Tien L. Dam, MD**, Division of Geriatric Medicine and Aging at NewYork-Presbyterian/The Allen Hospital and NewYork-Presbyterian/Columbia University Medical Center, and one of the study’s co-authors.

“Studies of older ICU survivors of mechanical ventilation have shown that many of these patients develop new deficits or increase the magnitude of pre-existing deficits associated with the frailty syndrome while critically ill,” says Dr. Baldwin. “These deficits, which may include malnutrition, weight loss, muscle wasting, and weakness, often persist after the critical illness resolves.”

The overall hypothesis of Dr. Baldwin’s research is that the outcomes of critical illness in older adults could be dramatically improved by understanding the determinants of those outcomes as well as the palliative care needs and treatment preferences of patients, and then by designing interventions based on that understanding during the post-ICU care period. “Since all these deficits are parts of the vicious cycle of frailty, measuring these frailty components in older ICU survivors may help risk-stratify and identify them for rehabilitative, therapeutic, or palliative interventions after an ICU stay,” says Dr. Baldwin.

In their investigation, Dr. Baldwin and his colleagues undertook a single-center prospective cohort pilot study of 22 medical ICU survivors age 65 years or older who had received noninvasive or invasive mechanical ventilation for at least 24 hours. “Our aim was to test the primary hypothesis that Fried’s frailty components could be measured in older ICU survivors of respiratory failure just prior to hospital discharge,” says Dr. Baldwin.

The researchers adhered to Dr. Fried’s widely adopted measures of physical frailty based upon five possible components – weight loss, weakness, slowness, reduced physical activity, and exhaustion. “The primary outcome was six-month mortality after the date of hospital discharge, and the secondary outcomes were disability related to dependency in activities of daily living – both those that had existed previously and those that followed after hospitalization.”

The investigators concluded that Fried’s frailty components can be measured in older ICU survivors of respiratory failure and that higher frailty scores at hospital discharge appear associated with higher risks of one-month disability and six-month mortality. “In this context, Fried’s frailty may represent a composite measure of an older ICU survivor’s physiologic reserve that is affected by pre-hospitalization health and disability, and the severity and duration of critical illness that he or she just survived,” says Dr. Baldwin.

Having critical information about a patient’s function and frailty status before coming into the ICU can well play a key role



Dr. Thuy-Tien L. Dam

in knowing how the patient will fare following discharge and their chances of survival.

“Geriatricians know that a major component of how well someone does in the ICU depends on how well they were before they came in. If they were robust, active, and functioning well, they might have the reserve to bounce back,” says Dr. Dam. “We also look at the trajectory of the patient’s progress. If you have someone who is declining quickly in the hospital, the likelihood of getting better after the ICU is much lower. And a patient admitted with an acute issue, such as a urinary tract infection or pneumonia, is more likely to do better than the person who has been declining over time prior to hospitalization. This may indicate that instead of doing everything in the ICU for this patient, perhaps you have goals of care discussions with the family about likelihood of recovery. It is a tough balance to want families to be realistic and yet for them to remain hopeful. It is even tougher when you don’t have data or evidence to support your discussion and decisions that need to be made.”

“This study has shown that if you were frail going into the ICU and coming out of the ICU, the likelihood of recovery is very low and actually the rate of mortality is very high,” adds Dr. Baldwin. “Using this evidence to start honest discussions with families will be helpful because you can provide them with data that helps support the future care decisions.”

### Reference Article

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## Bench to Bedside and Back to the Bench: Collaboration in the Medical ICU (continued from page 1)

the research into an animal model. “We created an A2 deficient mouse, and observed that these mice had tiny clots in the micro blood vessels,” says Dr. Hajjar. “In fact, we uncovered two important findings. First, the knockouts displayed the predicted accumulation of fibrin within blood vessels and, second, the mice exhibited defects in new blood vessel formation leading to the hypothesis that fibrinolysis and angiogenesis are functionally linked.”

Dr. Hajjar and her colleagues continued to study various aspects of the function of the protein on the mice, but ultimately her training as a physician – she is a pediatric hematologist – motivated her to want to understand whether this system had any relevance in human health and disease.

“I began to think about what would be a clinical setting in which this might be relevant, and sepsis came to mind,” notes Dr. Hajjar. “Annexin A2 is a protein that’s expressed on the surface of blood vessels and it helps to keep the blood in the fluid state. Patients with sepsis can have abnormalities in the fibrinolytic system and can develop a problem called disseminated intravascular coagulation, which can contribute to the high mortality rate that we see in sepsis.”

**“We know that in people who are extremely ill in the ICU, especially those with blood stream infections or sepsis, the blood clotting system is deranged. That is the landscape that we’re trying to understand with our hypothesis that annexin A2 might be playing a role in all of this.”**

**— Dr. Katherine A. Hajjar**

Dr. Hajjar sought out the expertise of Joseph T. Cooke, MD, and subsequently David A. Berlin, MD, Director of the Medical Intensive Care Unit at NewYork-Presbyterian/Weill Cornell, to help better understand the *in vivo* function of the A2 system.

“We know that in people who are extremely ill in the ICU, especially those with blood stream infections or sepsis, the blood clotting system is deranged,” says Dr. Hajjar. “The mystery about sepsis is that patients start off with a bloodstream



Dr. Katherine A. Hajjar

infection and then develop multiple organ failure. It’s not really clear why that happens. Oftentimes, if a patient does succumb, an autopsy will show no evidence of infection. In other words, antibiotics and other treatments have cleared the infection, and yet the patients still had catastrophic organ failure. It’s possible that there is something about the host response to the original infection that clears the infection but, at the same time, may lead to organ damage. That is the landscape that we’re trying to understand with our hypothesis that annexin A2 might be playing a role in all of this.”

The important message here, says Dr. Hajjar, is how their research was able to progress from the tissue culture dish to a small animal model and now to human studies due to collaborations with physicians who are providing the care to the patient. “By forming these types of partnerships, we can actually translate the findings that are occurring in the lab to the bedside and then back to the bench again,” says Dr. Hajjar. “In the lab, we have all this basic knowledge, but we don’t know whether it’s relevant to the clinical setting. With our colleagues in the ICU, we have been able to collect samples from very sick patients with sepsis, bring them back to our lab and analyze them. This has been quite informative. Not everything you see

in a tissue culture may be exactly the same as what occurs in a complex human body.”

To further the work in this area, Dr. Hajjar is planning to initiate preliminary experiments in a large animal model in collaboration with Paul M. Heerdt, MD, PhD, Professor of Anesthesiology. “In mice you can study what happens in the complete absence of a specific gene. But the response of a large animal model to major diseases such as sepsis may better approximate what we see in a human.”

Dr. Hajjar’s research program is focusing more and more on fundamental questions in biology that relate to human health and disease and providing training opportunities for medical students and fellows in translational projects. “It is important to form these linkages between clinical programs and the basic science labs so we can also train young scientists to do translational research,” says Dr. Hajjar. “One of the most interesting things about our lab is that we’re working at all three levels.”

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