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3 The Important Role of Ultrasound for Detecting Cancer in the Chest

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Addressing the Challenge of Diagnosing Sepsis

Sepsis, an overwhelming immune response to infection in the body, is a common critical care problem that affects hundreds of thousands of people in the United States every year and has a mortality rate in the 20 to 30 percent range.

Identifying sepsis early and then treating it aggressively improves outcomes for patients with sepsis who arrive in emergency rooms or for those who become septic while in a hospital inpatient unit. Yet, there is no simple test that enables physicians to make a rapid diagnosis of sepsis. “The criteria we use to diagnose



The streptococcus pneumoniae organism causes many types of pneumococcal infections, including sepsis.

sepsis are nonspecific,” says **Ann E. Tilley, MD**, a member of the Division of Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell Medical Center. “We look for signs such as fever or low body temperature, an elevated white blood cell count, and a heart rate or respiratory rate that is too fast.”

Patients who meet those specific criteria and also have an infection are categorized as having sepsis. Patients who also have organ system involvement are categorized as having severe sepsis. And if patients

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Bringing Expertise in Pulmonary Medicine to Ethiopia and Beyond

With a population of roughly 94 million people, Ethiopia is one of the largest countries in Africa, but also one of the poorest. It has fewer physicians per capita than almost any country in the world. The country has high rates of tuberculosis and acute respiratory infections and a significant but underappreciated burden of chronic obstructive lung disease and asthma, which are major public health problems. And yet the country had virtually no practicing pulmonary physicians and no pulmonary fellowship training program until now, thanks to **Neil W. Schluger, MD**, Chief, Division of Pulmonary, Allergy and Critical Care Medicine at NewYork-Presbyterian/Columbia University Medical Center. Dr. Schluger is leading an effort under the sponsorship of the World Lung Foundation to establish a pulmonary fellowship training program at Addis Ababa University School of Medicine.

A recent report from the World Bank notes that in efforts to improve health care delivery and outcomes in Ethiopia “the key constraint was the

lack of specialized doctors” to provide basic services at the primary and secondary care level. There is only one public sector lung health specialist in Ethiopia and the lack of pulmonary medicine physicians poses a significant obstacle to reducing morbidity and mortality from lung diseases.

“This program will fill a vital need,” says Dr. Schluger. “Our goal is to train pulmonologists in Ethiopia who will then be able to sustain a training program on their own.” In addition to the World Lung Foundation, established in 2004 to support private organizations and government

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Dr. Neil W. Schluger

Addressing the Challenge of Diagnosing Sepsis *(continued from page 1)*

manifest all of these symptoms concurrent with abnormally or dangerously low blood pressure, they are considered in septic shock, which carries the highest mortality rate.

“Early initiation of antibiotics is critically important for all these patients,” says Dr. Tilley. “Additional treatment is tailored to the specific patient’s situation. Most will need intravenous fluids and many will need vasopressors to support their blood pressure. Patients may also need blood transfusions as well as extra support for their lungs or kidneys, and other treatments depending on their particular organ dysfunction.”

Because this potentially life-threatening complication of an infection is so common and can be so deadly, researchers have been searching for blood biomarkers that would definitively point to a diagnosis of sepsis. Certain tests are used clinically, such as one that measures high lactate levels, which correlate with mortality in sepsis, and a procalcitonin test that can determine whether a patient has a bacterial infection. But, again, these tests are not, as Dr. Tilley points out, specific for sepsis and therefore do not provide a conclusive diagnosis.

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— Dr. Ann E. Tilley

The challenge to discover a method for identifying sepsis early escalated in New York State with the enactment of “Rory’s Regulations” – named after a 12-year-old boy who died from sepsis that went unrecognized in the emergency room where he presented after receiving a cut from a fall in his school’s gym. New York State was the first to adopt these regulations, which mandate that hospitals implement “evidence-based

protocols for the early recognition and treatment of patients with sepsis, severe sepsis and septic shock (sepsis protocols) that are based on generally accepted standards of care.”

To help achieve this, Dr. Tilley is leading a biomarker study to measure endothelial microparticles (EMP), which the Department of Genetic Medicine and the Division of Pulmonary Medicine had already been investigating for other medical conditions.

“We know that the endothelium in patients with sepsis becomes dysfunctional,” says Dr. Tilley. “So it makes sense for us to try to measure EMP as a potential tool for not only diagnosing sepsis, but also for predicting how people with sepsis would do down the line. Another element of this study involves looking at EMP levels over the first several days when the patients are critically ill to see if these levels can provide physicians with a way to measure whether the prescribed treatment is working or whether more aggressive therapy is necessary.”

The study is being conducted in collaboration with Weill Cornell Medical College-Qatar and Hamad Medical Corporation in Doha, Qatar, with a goal to enroll 450 patients at both sites over the next three years. According to Dr. Tilley, the study design is unique because many biomarker studies compare sick people to healthy people. “But that comparison is not clinically challenging for sepsis,” she notes. “What’s challenging is to tell the difference between a patient with sepsis and one who appears to be septic, but isn’t.” For that reason, the researchers would like to enroll every patient in the ICUs who have a suspected diagnosis of sepsis. “Once they are discharged we’ll go back and take a look at the data to ascertain that final diagnosis.”



Dr. Ann E. Tilley

The study is also collecting a significant amount of clinical information on its patients and their hospital course over time so the researchers can look at other factors that might affect either the patients’ mortality or their EMP values. When the data are collected, the researchers will use data from half of the subjects to determine whether septic patients are actually exhibiting different values or different trends over time.

“We will then use data from the second half of the population as an independent group of subjects to determine if the EMP values that appear to be predictive in the first group are actually predictive in the second group,” says Dr. Tilley. “Our goal is to develop a useful blood test that can assist doctors in taking care of their patients and counseling their families. Some of these patients are severely ill and may have other underlying conditions. They have a disease with a very high mortality rate and they’re undergoing a lot of very burdensome treatments. To be able to go to the families and say, ‘Based on this test your prognosis is terrific. We really should keep going even though this seems very burdensome,’ or ‘The prognosis is very grave despite our best efforts.’ That can help the families make the best choices for their loved ones.”

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The Important Role of Ultrasound for Detecting Cancer in the Chest

In just the past decade, the field of interventional bronchoscopy has made tremendous strides in the treatment of patients with pulmonary disease. In the Division of Pulmonary, Allergy and Critical Care Medicine at NewYork-Presbyterian/Columbia University Medical Center, **William A. Bulman, MD**, and **Roger A. Maxfield, MD**, and colleagues are employing the latest minimally invasive bronchoscopic techniques that are helping to diagnose and treat a wide range of lung disorders.

One of the most active areas of interest of the Columbia interventional pulmonary program is Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA), a relatively new minimally invasive procedure for sampling target lesions in the chest in patients who have suspicion of cancer or require staging of cancer, or have suspicion of either mediastinal or



Dr. William A. Bulman and Dr. Roger A. Maxfield

intrathoracic benign pulmonary disease. The technology combines bronchoscopic imaging with ultrasound imaging in order to look at the inside of the airways to identify targets that have been detected on radiologic imaging.

“EBUS-TBNA has gained wide acceptance as the preferred procedure for sampling intrathoracic lesions in patients with suspected or known lung cancer, often now supplanting surgical mediastinoscopy as a first-line approach,” says Dr. Bulman, Director of Bronchoscopy. “We use ultrasound guidance to do real-time sampling of targets, usually lymph nodes in the chest, but also lung masses, for the diagnosis or staging of lung cancer and other cancers that have spread to the chest. For individuals with suspected cancer and possible nodal involvement, diagnosis and staging can be performed by EBUS-TBNA in a single outpatient procedure, generally under moderate sedation.”

“With the use of live ultrasound imaging, you see the needle go into the lymph node or the mass that you’re sampling so there is no guesswork about the source of the tissue,” says Dr. Maxfield, Medical Director of the Interventional Bronchoscopy and Endobronchial Therapy Program. “Before the introduction of ultrasound we would look at a CT scan and have to estimate the best place to insert the needle, which had about a 50 percent success rate of hitting the target. If you didn’t get what you need the next step would be a surgical mediastinoscopy or a sampling of

the lymph nodes in open surgery. Now with real-time ultrasound, if the needle is not where you want it, you just redirect it. This avoids that additional surgical step. The last analysis of our diagnostic yield was approaching 95 percent.”

“For patients with a newly diagnosed lung cancer, we want to take a specimen from an area that will not only provide a diagnosis but also the stage of the cancer,” adds Dr. Bulman. “Our goal is to minimize the number of procedures a patient has to undergo and to provide information for treatment as efficiently as possible.”

“EBUS-TBNA helps to guide a patient’s treatment plan,” says Dr. Maxfield. “If a patient has a positive mediastinal lymph node initially, that patient will do better treated preoperatively with chemotherapy and often radiotherapy as well. If the lymph nodes are negative, that patient will do best going right to surgery.”

“Here at Columbia, we have developed expertise in this procedure, particularly in high risk patients, and have published a series of papers to describe our techniques for other practitioners who want to do EBUS-TBNA,” notes Dr. Bulman. “We have also published research describing our yield for the specialized molecular testing used for personalized treatment of lung cancer. If you identify a specific genetic abnormality for which there is a treatment, you can use targeted therapy, some of which have had some very dramatic responses even in advanced lung cancer. So identifying those molecular abnormalities is critical, and we’re able to do that with EBUS.”

“When we’re performing EBUS, a cytologist or a cytology technician is there with us,” says Dr. Maxfield. “As soon as we obtain a specimen, the cytologist does a quick stain and lets us know when we have sufficient tissue to make a diagnosis. We then obtain additional specimens for the molecular marker analysis. The time saved in confirming a diagnosis is significant.”

Dr. Bulman stresses that the interventional pulmonary team works in close collaboration with Columbia’s thoracic oncologists, radiation oncologists, radiologists, thoracic surgeons, and pulmonologists. “Our program is just one part of an intense multidisciplinary approach to lung cancer, which provides the optimal environment for diagnosing, treating, and curing patients with this disease.”

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Bringing Expertise in Pulmonary Medicine to Ethiopia and Beyond *(continued from page 1)*

agencies that work to improve lung health, predominantly in low- and middle-income countries, the pulmonary fellowship program is supported by the Swiss Lung Foundation and the Ethiopian Ministry of Health. Rotating faculty from Columbia University Medical Center, as well as several other U.S. academic medical centers, are physically present throughout the duration of the program, which is conducted at Black Lion Hospital, the largest public hospital in the country’s capital city. The first class of pulmonary fellows will graduate in 2015, and the program is expected to become self-sustaining within five years.

“The Ethiopian program is modeled after pulmonary fellowship programs here in the United States, including our own at Columbia,” says Dr. Schluger, who also serves as Chief Scientific Officer of the World Lung Foundation. “Fellows undergo a rigorous program of pulmonary medicine, with content specifically tailored to local hospitals and the population. We have a three-year intensive commitment to the program where we plan to train a

cohort of 10 pulmonary medicine physicians who will then know how to run their own training program. After that we intend to have a long-term affiliation and still be involved with training activities and research projects.”

The program’s research component is overseen by a Columbia faculty member. “We hope to be able to define the spectrum



The use of biomass fuel adds to lung problems in developing countries.

of lung disease specifically in Ethiopia, and we think that this information will have implications for Africa in general,” says Dr. Schluger.

The Columbia pulmonary medicine program is also reaching out to other countries in need of its expertise. “Half the people in the world, nearly all in resource poor countries, use biomass fuel – wood, charcoal, crop waste, and animal dung,” says Dr. Schluger. “These fuels burn inefficiently and produce significant amounts of smoke, which has a high concentration of air pollutants and adds significantly to the burden of both indoor and outdoor air pollution. One of our young faculty members is conducting a project in Ghana exploring how this problem can be addressed with better cookstove technology.” Dr. Schluger is also part of an epidemiologic study looking at the spread of tuberculosis in Kazakhstan.

“We are pleased to be able to share our knowledge and play an important role in global lung health,” adds Dr. Schluger.

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