The Division of Pulmonary, Allergy and Critical Care Medicine at UPMC

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We are proud to bring you the latest issue of *Respiratory Reader* with a focus on Acute Respiratory Distress Syndrome (ARDS). ARDS represents a life-threatening complication of inflammatory disorders including sepsis, trauma, pancreatitis, and pneumonia. Affecting 150,000 to 200,000 people in the United States each year, ARDS leads to death in as many as 45% of patients depending on severity. Despite intense investigation of ARDS pathophysiology and treatment, mortality has only slightly decreased in recent years. Current and future research is critically important to better define subphenotypes of ARDS to advance novel therapeutic options for this devastating syndrome. UPMC physicians and investigators at the University of Pittsburgh Acute Lung Injury Center of Excellence aim to provide state-of-the-art treatment to optimize chances of survival for these complex patients; to discover new and promising therapies to improve survival; to understand the recovery process; and to promote long-term functional recovery for survivors.

The Division of Pulmonary, Allergy and Critical Care Medicine operates one of the leading Pulmonary and Critical Care Medicine fellowship training programs in the country. Complementing our fellows' outstanding clinical training is exceptional scholarly development in all facets of biomedical research. Graduates of our program become leaders in community practice and in academic medicine, both at UPMC and at premier institutions across the country. They represent the next generation of physician investigators poised to take the treatment of critical illness and specifically ARDS to the next level.

In the pages that follow, you will learn about complications of influenza infection; state-of-the-art care for ARDS; application of point-of-care ultrasound in the intensive care unit; and innovative research at UPMC that is pioneering discovery for novel therapeutics for acute inflammatory diseases. Finally, you will meet the team of talented individuals who represent the Acute Lung Injury Center of Excellence and the expert clinicians in the Medical Intensive Care Unit at UPMC Presbyterian.

With great enthusiasm and respect,

Rama K. Mallampalli, MD

Chief, Division of Pulmonary, Allergy and Critical Care Medicine

UPMC Endowed Professor and Director, Acute Lung Injury Center of Excellence at the University of Pittsburgh

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Affiliated with the University of Pittsburgh School of Medicine, UPMC is ranked among the nation's best hospitals by *U.S. News & World Report*.

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State-of-the-Art Care for Every ARDS Patient

At UPMC, we offer the most current therapies for patients with Acute Respiratory Distress Syndrome (ARDS). Optimal provision of supportive care includes low tidal volume mechanical ventilation, conservative fluid management, attention to control of hyperglycemia, and conservative use of blood product transfusions. A subset of patients with ARDS will experience severe and refractory impairment in their ability to oxygenate the blood, placing them at significantly increased risk of death from the disorder. Several advanced interventions have been proposed to improve mortality in this population including high positive end-expiratory pressure, muscle relaxation, prone positioning, and extracorporeal membrane oxygenation (ECMO). Alternative treatments may improve oxygenation, but the effect on survival is not as well defined, for example with use of inhaled pulmonary vasodilator therapy. Since predicting which patients will fare poorly is not possible at the onset of disease, early referral to a tertiary center with expertise delivering these modalities and studying their impact is essential to optimize the chances of survival and recovery. At UPMC, we have extensive experience with provision of each of these life-sustaining measures to the appropriate patients, and we are involved in cutting-edge investigations to advance the care of the severely ill ARDS population.

Cutting-edge Clinical and Translational Research Exploring Novel Therapeutics

ARDS patients have different phenotypes representing variability in how the lung injury evolves in response to an inflammatory insult. Such variability complicates the design of studies and limits the interpretation and application of data from clinical investigations. At UPMC, we have developed the Acute Lung Injury Registry and Biospecimen Repository to better understand the natural history and varying phenotypic presentation of ARDS. This will also facilitate development of targeted therapeutics in the future, ultimately enabling clinicians to personalize the approach to treatment of patients with ARDS. Patients who participate in this registry will help future patients by providing data for planning and piloting potential therapeutic studies.

In addition, UPMC physicians are involved in large-scale clinical trials for the treatment of ARDS. We are currently enrolling patients in a National Institutes of Health-sponsored Phase I/II, multicenter, randomized, double-blinded, placebo controlled study exploring Allogeneic Bone Marrow-Derived Human Mesenchymal Stem Cells for the treatment of Acute Respiratory Distress Syndrome. Similarly, as a member of the NIH-sponsored Prevention and Early Treatment of Acute Lung Injury (PETAL) Network, UPMC physicians are recruiting subjects for a large Phase III study, Reevaluation

Dr. Tomeka Suber practices point-of-care ultrasound during Dr. Phillip Lamberty's critical care ultrasound training course.

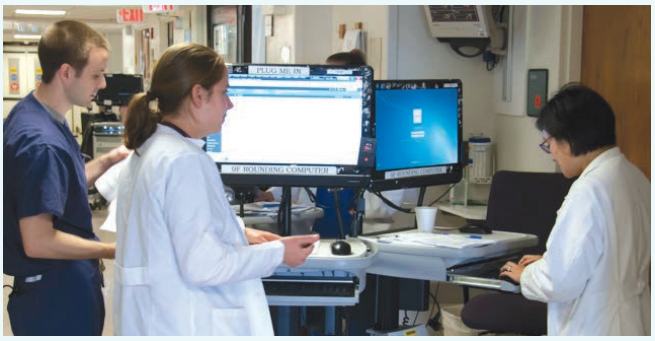
of Systemic Early Neuromuscular Blockade (ROSE), confirming the benefit of early muscle relaxation in severe ARDS, and will participate in multicenter prevention trials in the near future.

Complementing clinical practice and bedside investigations at the University of Pittsburgh Acute Lung Injury (ALI) Center of Excellence, we have an experienced team of scientists exploring the mechanisms of disease at its earliest discovery in search of novel therapeutic targets and strategies for future translation to patient care. ALI investigators are well funded by the National Institutes of Health and represent leaders in the fields of lipid biology, alveolar barrier regulation, pulmonary vascular physiology, innate immunity, and inflammation, providing a unique and collaborative approach to mechanistic exploration in the laboratory and translation to the patient care. In addition, we are developing industry partnerships and designing pilot therapeutic and observational studies.

Investigator Spotlight

Janet S. Lee, MD, is professor of medicine in the Division of Pulmonary, Allergy and Critical Care Medicine. Her laboratory investigates the biology of critical illness and host determinants of lung injury. Key questions that define her research program center on the host response to infection-induced injury that underlies ARDS and sepsis.

Dr. Lee is interested in how the host recognizes and responds to products of extracellular gram negative pathogens such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, common nosocomial pathogens that cause acute lower respiratory tract infections in intensive care unit patients with respiratory failure and requiring mechanical ventilation. She recently showed that a host protein called CD36 expressed on the surface of macrophages, blood vessels, and platelets is involved in providing defense against pneumonia in mice from *K. pneumoniae*.[1] The main mechanism of *K. pneumoniae* pathogenicity is its ability to evade serum killing and escape phagocytosis. While virulent strains of *K. pneumonaie* cause invasive syndromes in humans, multidrug-resistant (MDR) carbapenamase-producing *K. pneumoniae* clinical isolates found in ICUs are relatively avirulent in mice and are easily killed by serum from healthy volunteers. This finding prompted Dr. Lee and her group to embark upon studies to determine whether they can identify ICU patients within the UPMC Acute Lung Injury Registry and Biospecimen Repository whose serum was unable to kill MDR *K. pneumoniae*. They will then examine whether defects in serum killing of MDR *K. pneumoniae* are broader markers of a relative immunosuppressed state following overwhelming critical illness.



Dr. Janet Lee (right) leads rounds in the UPMC Presbyterian Medical Intensive Care Unit.

Another focus of Dr. Lee's laboratory is how the host protects against aggressive lung injury triggered by *P. aeruginosa* through the release of soluble factors from injured blood vessels and platelets. When this protective mechanism goes awry, such as in the case when platelet counts fall below a threshold level during overwhelming critical illness, the host is unable to adequately repair the air sacs responsible for gas exchange. Studying the precise mechanisms underlying this defect will enable identification of potential targets to combat ARDS and overwhelming sepsis in the future.

Beibei (Bill) Chen, PhD, is associate professor of medicine in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Pittsburgh. He is co-director of the Acute Lung Injury Center of Excellence and director of the PACCM Center for Small Molecule Therapeutics. His primary research interest includes the study of the molecular mechanisms that control lung injury and fibrosis via the regulation of protein breakdown. Specifically, over the last four years, Dr. Chen has successfully identified and characterized more than 10 novel enzymes that regulate protein processing termed ubiquitin E3 ligases. His work has been published in top-tier journals related to protein ubiquitination including *Nature Immunology, Nature Medicine, Cell Reports, Science Translational Medicine, Journal of Experimental Medicine, and eLife*.

His second area of research interest is in the design of small molecule therapeutic agents. Dr. Chen has submitted 10 provisional patents related to novel anti-inflammatory and anti-fibrotic compounds, and he has successfully designed and synthesized a unique series of first-in-class small molecule E3 ligase inhibitors. One of his molecules has passed preclinical pharmacokinetic and toxicity studies and is on track for Phase I safety evaluation in human subjects with exacerbations of chronic obstructive pulmonary disease (COPD) in 2017.

Dr. Chen's long-term goal is to develop a new class of therapeutics that combats pulmonary diseases by focusing on distinct mechanisms. To this end, with the support of the division, he recently established the PACCM Center for Small Molecule Therapeutics to increase scientific understanding and collaborative efforts to develop new chemical entities or compounds that target various pulmonary diseases including ARDS, asthma, pulmonary fibrosis, COPD, and lung transplant rejection. Please visit the Center website at www.dom.pitt.edu/PACCM/centers-institutes/SmallMoleculeTherapeutics.html for more information.

Dr. Bill Chen (right) discusses small molecule therapeutics with a group of trainees and laboratory personnel.

Sepsis-Induced Cardiomyopathy and the Application of Point-of-Care Ultrasound in the Intensive Care Unit

Ian J. Barbash, MD

Phillip E. Lamberty, MD

A previously healthy 50-year-old woman presented to the UPMC Presbyterian Emergency Department with dyspnea, pleuritic chest pain, rust-colored purulent sputum, and hypotension. She had been tending to her hospitalized son for weeks as he recovered from neurological surgery. Her chest radiograph confirmed a right-sided lobar pneumonia. She was rapidly resuscitated with several liters of intravenous crystalloid fluid and required oxygen via high-flow nasal cannula. Broad spectrum antibiotics were administered and she was admitted to the medical intensive care unit. She quickly developed respiratory distress requiring endotracheal intubation, after which she developed hypotension unresponsive to additional crystalloid boluses. A norepinephrine infusion was started. Her vasopressor requirements increased steadily, and she developed anuria and skin mottling. Whole body ultrasonography consisting of lung imaging, a focused cardiac ultrasound, limited abdominal imaging, and scanning of the lower extremity proximal deep veins also was performed.

Chest scanning revealed consolidation of the right lower lobe without significant pleural fluid (Figure 1). Cardiac views were limited, but subcostal images revealed severe global left ventricular dysfunction and preserved right ventricular function (Figure 2, and video QR code on page 5). Given the protean manifestations of septic shock, a presumptive diagnosis of sepsis-induced cardiomyopathy was made. A dobutamine infusion was initiated with improvement in perfusion as determined by lactate clearance, increased urine output, and improved mental status. Blood cultures rapidly grew group A *streptococcus* and antibiotics were tailored appropriately. Both norepinephrine and dobutamine infusions were weaned off over the next 48 hours. Serial cardiac ultrasound examinations demonstrated improvement in left ventricular function over the ensuing days (see video QR code on page 5) without development of a significant pleural fluid collection. She was successfully liberated from mechanical ventilation within four days and sustained a full recovery.

As many as 50% of patients with severe sepsis or septic shock may exhibit myocardial dysfunction.[1] Advances in ultrasound technology provide clinicians with a portable, dynamic, real-time imaging device readily applicable to patient care at the bedside. As a result, point-of-care ultrasound (POCUS) assessment has recently evolved as an extension of the physical exam and diagnostic assessment for critically ill patients. With a combination of didactic instruction, simulation, and hands-on application, trainees and experienced clinicians can gain competence in image acquisition and interpretation in order to recognize specific diagnoses with important therapeutic implications. The purpose of POCUS is not to replace formal diagnostic ultrasonography, but rather to expand the "toolkit" available to clinicians caring for critically ill patients. Here we discuss how physicians in the medical intensive care unit (MICU) at UPMC Presbyterian apply POCUS in a variety of anatomic domains to enhance diagnostic accuracy and therapeutic quality for a broad range of clinical problems.

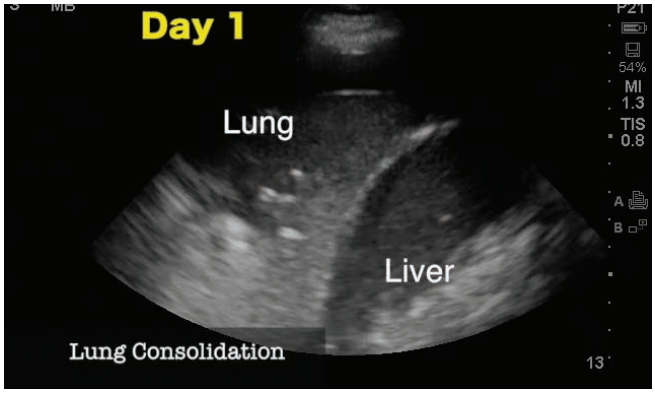


Figure 1: *Transthoracic image depicting the consolidation "tissue sign" of the right lower lobe of the lung.*

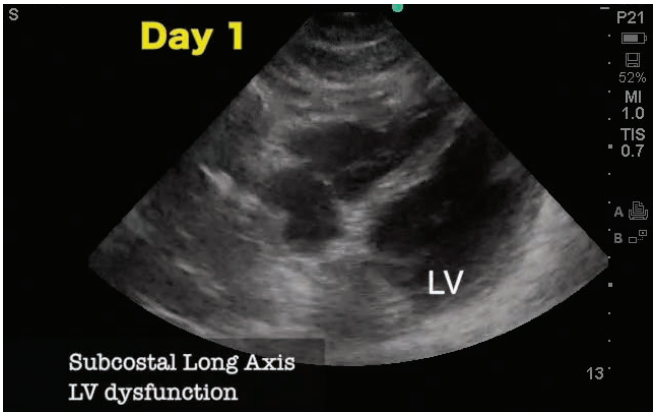


Figure 2: *Subcostal cardiac image demonstrating severe LV systolic dysfunction while on norepinephrine infusion.*

Cardiac Ultrasound

Focused cardiac ultrasound (FCU) is an invaluable component of the evaluation of a critically ill patient, particularly for patients in shock. In contrast to the more involved approach necessary for formal echocardiography, FCU involves the acquisition and primarily qualitative interpretation of images from a limited number of ultrasound windows. The FCU exam typically includes parasternal (long and short axis), subcostal, and four-chamber apical views, although the latter apical views may be challenging to obtain in critically ill patients. These images allow the intensivist to identify a number of findings that facilitate diagnosis and management of patients in shock (Table 1). Importantly, because of variation in the quality of image acquisition and interpretation, most FCU findings require confirmation via formal echocardiography before they are used to trigger invasive therapeutic interventions.

Table 1. *Focused Cardiac Ultrasound Findings and Implications*

Cardiac Ultrasound Finding	Diagnostic Implications	Therapeutic Implications
Impaired LV function	Ischemic or non-ischemic cardiomyopathy	Inotropes, coronary angiography, mechanical support
Dilated/impaired RV function	Pulmonary hypertension, possible pulmonary embolism	Pulmonary vasodilators, possible need for thrombolytic therapy
Pericardial effusion	Possible pericardial tamponade	May require pericardiocentesis
IVC size and variation	Hypovolemia/ volume responsiveness	Cardiac output may improve with increased intravascular volume
LV=left ventricle; RV=right ventricle; IVC=inferior vena cava		

Thoracic Ultrasound

Bedside ultrasound is now the standard of care in the diagnosis and management of pleural diseases. Using ultrasound, our ICU physicians can detect and distinguish between varieties of conditions, including pleural effusions, atelectasis, and consolidated lung (Figure 1); in so doing clinicians may avoid unnecessary CT scans. Additionally, all pleural drainage procedures are performed with ultrasound guidance at the point of care, and often in real time. With supervision from an experienced provider, this approach significantly reduces potential complications of pleural drainage procedures. Finally, as ultrasound is readily available in our ICU, faculty and fellows often use the presence of lung sliding on ultrasound (which indicates an intact interface between the lung and chest wall) to rule out pneumothorax as a cause of clinical deterioration in mechanically ventilated patients.

Abdominal and Vascular Ultrasound

In addition to cardiac and thoracic imaging, ultrasound is useful for abdominal and vascular diagnosis and procedural guidance. Using ultrasound, ICU physicians can detect abdominal ascites and obstructive uropathies (indicated by the presence of hydronephrosis or a distended bladder). Physicians inside and outside the ICU routinely confirm the presence and location of ascites prior to diagnostic or therapeutic paracentesis. Using the linear array probe, ultrasound permits diagnosis of deep venous thrombosis in the proximal large vessels of the upper or lower extremities and is invaluable for performance of vascular access procedures in all locations. Often, when patients simply need peripheral IV access, clinicians are successful with an ultrasound-guided approach when other attempts fail, thereby avoiding unnecessary central line procedures. Real-time ultrasound guidance is considered the standard of care during central venous catheter placement, and can also provide a useful adjunct during difficult arterial line placement.

Ultrasound Training

All trainees rotating through the UPMC Presbyterian Medical ICU receive formal instruction in ultrasound techniques. During their first year, interns in the ICU complete a central line training course involving ultrasound imaging of real patients and ultrasound-guided procedural practice in simulation. This training prepares them to perform bedside procedures under the supervision of expert faculty and fellows. At the beginning of the fellowship program, incoming fellows undergo several days of intensive ultrasound training, including cardiac, thoracic, abdominal, and vascular imaging. Their ultrasound instruction continues throughout fellowship, via formal ultrasound noon conferences, bedside procedures, and participation as instructors for resident ultrasound training courses. Phillip Lamberty, MD, leads an effort to expand training in the responsible use of ultrasound in the Division of PACCM, the Department of Medicine, and the medical community at large. In concert with colleagues in the Department of Emergency Medicine, he offers a two-day course on cardiac, lung, abdominal, and vascular ultrasound acquisition and interpretation. The Introduction to Emergency and Critical Care Ultrasound (IECCUS) course incorporates simulation, scanning of standardized patients, and interactive case reviews enabling participants to begin to implement point-of-care ultrasound in their everyday practice. The course will be offered in the fall of 2017. To register, visit goo.gl/A7s4V9.

Summary

In conclusion, bedside ultrasound is an increasingly ubiquitous component of the training and practice of pulmonary and critical care medicine. UPMC Presbyterian faculty and fellows routinely use ultrasound in the diagnosis and management of critically ill patients, frequently changing and improving patient care based on their ultrasound findings.

Scan with a smartphone or tablet QR reader to see the ultrasound video images or go to: vimeo.com/193460170

Complications of H1N1 Infection with ARDS

William Bain, MD

Bryan J. McVerry, MD

A 56-year-old man recently discharged from an alcohol rehabilitation facility presented to the UPMC Shadyside Emergency Department with two days of cough, dyspnea, and vomiting. Review of systems was notable for weakness, subjective fever, and chills. In addition, he reported multiple sick contacts with similar symptoms encountered at the rehab facility. In the emergency department, he was febrile (39.4C) and tachycardic (118 beats/minute). His chest radiograph revealed diffuse patchy consolidation suggestive of multifocal pneumonia (Figure 1). He was admitted to the general medical floor and antibiotics were initiated with ampicillin-sulbactam and azithromycin for treatment of community-acquired pneumonia. Shortly after admission, the patient's clinical condition deteriorated, his oxygen requirement rapidly increased, and he developed hemoptysis. Oseltamivir was added to the patient's antimicrobial regimen for concern for influenza A, and he was transferred to the medical intensive care unit (MICU).

In the MICU, he was administered conscious sedation and underwent bronchoscopy with bronchoalveolar lavage (BAL). During the ensuing 24 hours, his hypoxemia worsened and he was intubated and mechanically ventilated for severe acute respiratory distress syndrome (ARDS). He received low-tidal volume ventilation (6cc/kg predicted body weight)[1]; high positive end-expiratory pressure[2] (PEEP = 16cm H2O), deep sedation with neuromuscular blockade using cisatracurium,[3] prone positioning,[4] and inhaled epoprostenol. On hospital day three, his BAL specimen revealed H1N1 influenza A, influenza B, and adenovirus. Oseltamivir was transitioned to intravenous peramivir to complete a 10-day course of neuraminidase inhibition. With the exception of leukocytosis and fever on hospital day 12 due to methicillin-sensitive *Staphylococcus aureus* in his sputum treated with cephalexin, he had no further evidence of infection. Following conservative fluid balance guidelines,[5] he received aggressive diuresis with improvement in his respiratory status over the following six days.

He continued to do well from a respiratory standpoint, and his sedation was decreased to allow spontaneous breathing trials. On hospital day 10, he demonstrated short periods of tachycardia, hypertension, tachypnea with hyperpnea, and abnormal upper extremity movement. Electroencephalogram (EEG) was negative for seizure, and the episodes were attributed to agitated delirium. Despite aggressive efforts to treat delirium, the events continued and became associated with dysautonomia leading to trials of nicardipine and esmolol infusion to control severe hypertension. Brain MRI on hospital day 20 (Figure 2) revealed acute disseminated encephalomyelitis (ADEM), a post-infectious autoimmune demyelinating disease. Despite sequential therapy with intravenous immunoglobulin therapy, plasmapheresis, and pulse dose steroids for three days followed by an extended steroid taper,[6,7,8] he sustained minimal functional neurologic recovery, and was discharged to a skilled nursing facility on hospital day 60 for subacute rehabilitation and weaning from mechanical ventilation.

Influenza A is the second most common pathogen detected in adult patients requiring hospitalization with community-acquired pneumonia.[9] The H1N1 strain of influenza A caused the 2009 "swine flu" pandemic and was the predominant influenza strain circulating during the 2015-2016 season.[10] Although many strains of influenza can cause significant morbidity and mortality, the H1N1 strain is particularly virulent and is associated with a younger patient population, more severe illness, and worse outcomes

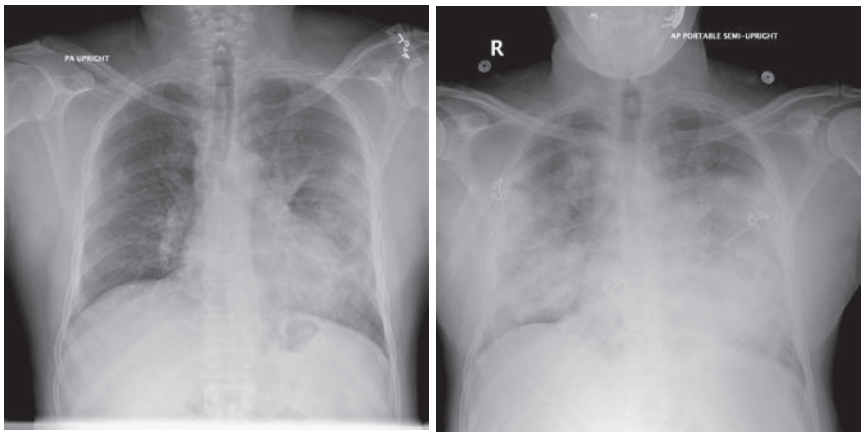


Figure 1: *Chest radiograph at ED presentation and hospital day 3 showing progression to severe ARDS.*

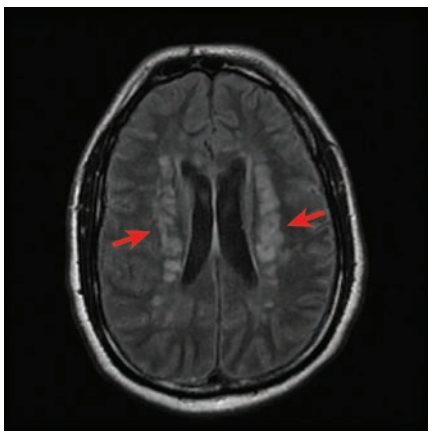


Figure 2: *MRI Brain T2 FLAIR image demonstrating demyelination (red arrows).*

including increased mortality.[11] The most severe complications of H1N1 include ARDS, bacterial superinfection, thrombophilia, cardiovascular involvement such as myocarditis, and neurologic manifestations such as encephalitis.

ARDS is commonly associated with severe pneumonia, including H1N1 and other viral and bacterial pathogens. The ARDS clinical syndrome is defined by non-specific features including: (1) progressive hypoxemic respiratory failure within one week of exposure to a definable risk factor (Table 1); (2) diffuse bilateral alveolar infiltrates on chest radiograph not attributable to alternative etiology such as heart failure or atelectasis; and (3) severe hypoxemia (PaO2/FiO2 ratio < 300 for mild, < 200 for moderate, and < 100 for severe). Although there are no direct therapies for ARDS, high-quality supportive care highlighted in the case above has improved overall mortality in ARDS. Low tidal volume ventilation (6cc/kg predicted body weight, goal plateau pressure < 30 cm H_2O) is a fundamental protective therapy that has demonstrated improved mortality in multiple high-quality investigations.[1] In patients with severe ARDS, neuromuscular blockade after deep sedation and early prone positioning have both demonstrated improved mortality in single high-quality randomized clinical trials.[3,4] Finally, referral to an extra-corporeal membrane oxygenation (ECMO) center such as UPMC Presbyterian may be beneficial for patients with severe respiratory failure.[12] Despite improved supportive care, mortality in ARDS remains near 40%, which highlights the need for further investigation. Clinicians and investigators at UPMC and the University of Pittsburgh Acute Lung Injury Center of Excellence are actively engaged in mechanistic and therapeutic studies targeting improved care for ARDS patients.

Table 1: *Common Risk Factors for Acute Respiratory Distress Syndrome.*

Direct Lung Injury	Indirect Lung Injury
Infectious pneumonia	Sepsis
Aspiration	Trauma
Near drowning	Blood product transfusion
Smoke or other toxic inhalation	Pancreatitis
Pulmonary contusion	Burn
Cardiothoracic surgery	Drug overdose

Bacterial superinfection is a common respiratory complication of influenza, including H1N1. The offending pathogens are typically Gram-positive bacteria, most commonly *Streptococcus pneumoniae* and *Staphylococcus aureus* that manifest approximately seven days after initial influenza infection. Common clinical signs include fever after a period of normal temperatures, leukocytosis, radiographic lobar pneumonia, and sputum Gram stain exhibiting bacterial pathogens. Treatment includes broad-spectrum antibiotics with particular attention to Gram-positive organisms narrowed once clinical microbiologic data is available. Interestingly, the H1N1 strain may also predispose patients to invasive *Aspergillus fumigatus* infection. Multiple reports from the 2009 pandemic, including a series from UPMC,[13] described invasive aspergillosis in patients without any evidence of immune suppression prior to their hospitalization with H1N1 influenza. The underlying etiology of the increased susceptibility to bacterial pneumonia after influenza is actively being investigated in the Division of Pulmonary, Allergy and Critical Care Medicine at UPMC, which may yield novel therapeutics in the coming years. Until then, it is important for clinicians to remain vigilant for bacterial pneumonia following influenza infection.[14,15,16]

Although less common than bacterial superinfection, evidence supporting the notion that H1N1 influenza may increase the risk of thromboembolism is accumulating. A Canadian study reported a 6% incidence of thrombosis despite prophylactic anticoagulation in a cohort of patients with pandemic H1N1 in 2009.[17] Interestingly, three of these patients experienced arterial thrombosis. Further investigation is warranted, but such reports direct attention to the importance of prophylactic anticoagulation in critically ill patients.

Influenza has long been associated with increased cardiovascular morbidity and mortality,[18] which is thought to result from aggravation of underlying cardiac disease and from direct myocardial involvement.[19] The mainstay of therapy in patients with underlying cardiac disease remains prevention through influenza vaccination, which has been shown to decrease cardiovascular mortality.[20] Direct cardiac involvement of influenza can present as an acute viral myocarditis. In fact, influenza A was identified in up to 10% of cases with an endomyocardial biopsy-proven viral etiology.[19] Numerous case reports have described acute fulminant viral myocarditis due to the H1N1 strain of influenza — notably, it is reported to affect a younger patient population.[21,22] Fulminant myocarditis due to influenza typically occurs within two weeks of influenza symptoms and manifests as impaired ventricular function often leading to cardiogenic shock requiring circulatory support such as ECMO.[23] Although mortality in H1N1 fulminant myocarditis has been reported to be 24%, rapid and complete recovery has been described.[23]

Finally, as described in the case above, H1N1 influenza may be associated with severe neurologic complications. A wide range of reported influenza-associated neurologic complications has been described, but the most robust data comes from a population-based study in California during the 2009 H1N1 pandemic.[24] In this cohort of more than 2,000 patients with severe H1N1, 3.7% were classified as developing primary neurologic complications, approximately one-third of whom (1.4% of total population) were diagnosed with severe encephalitis or encephalopathy. Although it is rare, acute disseminated encephalomyelitis has been described in association with influenza,[25] and H1N1 influenza was felt to be the most likely etiology of this patient's severe neurologic injury.

In conclusion, H1N1 and other strains of influenza may lead to severe morbidity and mortality through both respiratory and extra-pulmonary complications. Therefore, early referral to tertiary care centers with access to advanced rescue therapies, 24-hour multidisciplinary physician support, cutting-edge respiratory therapy support, and specialized ICU nursing care such as at UPMC Presbyterian can be lifesaving.

State-of-the-Art Sepsis Treatment: A Review

Andrea Levine, MD

Meghan Fitzpatrick, MD

Sepsis is among the most frequently encountered diagnoses in the intensive care unit (ICU). Despite time trends of improvement in mortality, sepsis is the second leading cause of death among non-cardiac ICU patients, and is the 10th leading cause of death in the United States.[1] In 2013, there were 1.2 million hospital stays associated with sepsis, and sepsis was the most expensive condition treated in U.S. hospitals at a cost of $23.6 billion/year.[2,3] For these reasons, sepsis has been afforded particular attention in an effort to decrease its substantial burden of morbidity and mortality. More stringent delivery of established therapies via protocols has demonstrated diminished returns in the modern era, highlighting the need for novel methods of detecting, assessing, and treating the syndrome.[4,5]

Establishing a standard definition for sepsis is crucial to assuring reliable recognition and creating a reliable foundation for development and interpretation of research. In 1989, Roger C. Bone introduced the modern definition of sepsis as "an invasion of microorganisms and/or their toxins into the bloodstream, along with the organism's reaction against this invasion."[6] In 1991, a consensus statement, Sepsis-1, was drafted by the American College of Chest Physicians and the Society of Critical Care Medicine. This statement established sepsis as a spectrum of disease ranging from Systemic Inflammatory Response Syndrome (SIRS) to septic shock. The criteria set forth in Sepsis-1 was widely accepted for more than two decades (Table 1).[7]

Table 1: *Criteria for Sepsis.*

Diagnosis	Definition
Sepsis-1	
SIRS (Systemic Inflammatory Response Syndrome)	• Two or more of the following criteria: 1) Temperature > 38 or < 36 2) Heart rate > 90 3) WBC > 12 or < 4 or 10% bands 4) Respiratory rate> 20/min or PaCo2 < 32
Sepsis	• SIRS with presumed or proven infection
Severe sepsis	• Sepsis with evidence of end organ dysfunction
Septic shock	• Severe sepsis refractory to fluid resuscitation
Sepsis-3	
Sepsis	• Life-threatening organ dysfunction caused by a dysregulated host response to infection. • SOFA score ≥ 2
Septic Shock	• Sepsis AND • Persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation

In 2014, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine assembled 19 critical care, infectious disease, surgical, and pulmonary sepsis experts to redefine sepsis (Sepsis-3, Table 1). The resulting definitions emphasize the pathophysiology of sepsis as an interaction between the host and the pathogen and recognize the balance between host pro- and anti-inflammatory responses. The new guidelines eliminate the SIRS criteria, due to both lack of specificity and lack of robust association with significant morbidity or mortality. "Severe sepsis" is eliminated due to a dearth of universally accepted guidelines that define or quantify "end organ dysfunction."[8] Per Sepsis-3, sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection." The SIRS criteria are recognized as supporting evidence for an underlying infection. The inclusion of "life-threatening organ dysfunction" is critical in the new definition of sepsis and highlights the role of ongoing organ-specific cellular defects.[8] Septic shock is newly defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality." The combination of both vasopressor requirements and persistent lactic acidosis recapitulates the circulatory and cellular dysfunction that characterize the new definition of septic shock.

The Sequential Organ Failure Assessment (SOFA) and qSOFA (Table 2) are now recommended means of quantitatively, objectively, and consistently assessing patients with presumed infection for sepsis. In ICU patients with suspected infection, the use of the raw SOFA score or a change in the SOFA score of two points better discriminates hospital mortality compared to SIRS criteria. In non-ICU patients, the SIRS criteria and the SOFA score are comparable. Patients with a SOFA score of 2 or more had an estimated 10% mortality.[8] Because the SOFA score depends on laboratory data that may not be available at the time of patient evaluation, a modified score, "qSOFA," was proposed as a rapid bedside screen.[8,9] The qSOFA includes only three components: 1) systolic blood pressure of < 100 mm Hg; 2) respiratory rate > 22/minute; and 3) altered mental status, and compares well to the SOFA. If two of these three variables are present, further evaluation for end-organ damage is warranted.

Future diagnostic approaches in the field of sepsis are likely to involve strategies that can define sepsis earlier than culture data and SOFA criteria, including identification of biomarkers and alternative methods of pathogen detection. Non-specific

inflammatory biomarkers such as CRP and procalcitonin (PCT) are available in many clinical laboratories and have been extensively studied. Both biomarkers are elevated in infection and may be linked to outcomes, but whether abnormal levels are actionable to improve identification or management of septic patients remains unclear. Other investigational biomarkers that may serve as effective predictors of mortality and disease severity include pro- and anti-inflammatory cytokines, endothelial markers (including angiopoietin 1 and 2 and endocan), and leukocyte surface markers.[10] Finally, functional genomics and gene expression profiling have the potential to differentiate an adaptive immune response from sepsis and potentially to identify a pattern of gene expression as a "fingerprint" for sepsis,[11] and evolving point-of-care next generation sequencing techniques and devices hold promise for rapid pathogen identification and antibiotic susceptibility prediction.[12, 13]

Table 2: *Severity Assessment in Sepsis.*

SOFA	qSOFA
PaO2/FiO2 ratio	Respiratory rate > 22
Blood pressure	Systolic blood pressure < 100mmHg
Glasgow Coma Scale (GCS)	Altered mental status
Bilirubin	
Creatinine	
Urine output	

Despite the recent redefinition of sepsis, the standard interventions remain early fluid resuscitation, early and appropriate treatment of infection, and administration of vasopressors.[14, 15, 16] Controversy persists regarding the optimal volume of fluid resuscitation, the most effective and reliable way to assess a patient's volume status, and how to predict hemodynamic susceptibility to volume resuscitation (i.e. volume responsiveness). Only 50% of patients will respond to volume expansion with an increase in the cardiac output, regardless of their fluid status;[17] therefore, determining volume status alone is insufficient. In the post-pulmonary artery catheter era, various modalities have been proposed to assess volume status and fluid responsiveness. Pulse pressure variation (PPV), as assessed on an arterial line, is an effective way to determine volume responsiveness in both spontaneously breathing and mechanically ventilated patients with a regular cardiac rhythm.[17] Additional methods include a passive leg raise (PLR) in conjunction with PPV or continuous invasive or non-invasive cardiac output monitoring. However, the mechanics of performing such maneuvers in medically complex, unstable patients limits the universal acceptance of such diagnostic strategies.[18] More sophisticated point-of-care ultrasound techniques can aid in the assessment of volume responsiveness. The use of ultrasound-guided IVC measurements was transiently popular but has come under increasing scrutiny due to limitations including the often non-diagnostic IVC diameter and the inability to use IVC measurement in spontaneously breathing patients. Cardiac output can also be assessed via a cardiac 5-chamber view on transthoracic echocardiogram (see related feature on page 4). Combining cardiac ultrasound with a PLR is another sophisticated, albeit logistically challenging, technique for measuring volume responsiveness with high specificity and sensitivity.[19] Finally, ultrasound measurement of carotid blood flow, an additional surrogate for stroke volume, can predict fluid responsiveness and requires less ultrasound skill than cardiac velocity time integral (VTI). Studies have shown that the carotid blood flow variation more accurately predicts volume responsiveness than stroke volume variation, passive leg raise in combination with pulse pressure variation, pulse pressure variation, change in IVC diameter, or central venous pressure.[20] While these ultrasound-based strategies are valuable for assessing patients' volume responsiveness, they rely on a high level of ultrasound training to obtain meaningful and interpretable results.

The inflammatory dysregulation of sepsis represents an ongoing investigational diagnostic and therapeutic target. To date, despite data supporting the role of inflammatory pathways and mediators in the evolution and resolution of sepsis, no convincing data support the routine use of steroids or immunomodulatory therapeutics for the treatment of sepsis. One of the more exciting future potential therapies in this arena is mesenchymal stem cell (MSC) transfer. MSCs have differentiation potential, capacity to modulate immune responses, pro-angiogenic and repair capacity, and low immunogenicity. These cells can regulate immune cells and are, themselves, activated by inflammatory cytokines, which are markedly elevated in patients with sepsis. MSCs use inflammatory cytokines and chemokines as homing signals to detect ongoing inflammation and to localize to the involved tissues. Animal studies using MSCs in sepsis have demonstrated a reduction in overall organ dysfunction (kidney, liver, spleen, pancreas, lung, and heart), a lower number of neutrophils to target organs, and a lower burden of pro-inflammatory cytokines.[21] Regarding microbial burden, the use of MSCs demonstrates increased antimicrobial properties, increased phagocytic properties of neutrophils, monocytes, and macrophages, and overall an improved bacterial clearance.[21] Additional therapeutic agents in development for sepsis include small molecule immunomodulators, which are currently under investigation at the University of Pittsburgh Acute Lung Injury Center of Excellence (see feature on page 3). Such therapeutics, when combined with novel biomarker assessments, have the potential to precisely target the dysfunctional immune response in a given patient with a given sepsis phenotype and precision therapeutics for sepsis.

Questions and controversies remain regarding the pathophysiology, diagnosis, and treatment of sepsis despite descriptions of sepsis dating back to the time of Hippocrates. The newest framework of sepsis is useful at the bedside in that it emphasizes early recognition of a life-threatening and pathologic level of inflammation resulting in organ damage, and highlights the needs for early intervention. Future management strategies will likely include enhanced assessment of circulatory pathophysiology and the patient's inflammatory response guiding targeted intervention to rectify the underlying inflammatory dysregulation. Until such time, intensivists and health systems would do well to continue to vigilantly screen for sepsis and reliably deliver the few proven therapies, while making use of new clinical tools such as ultrasound or novel biomarker assessments as they become available.

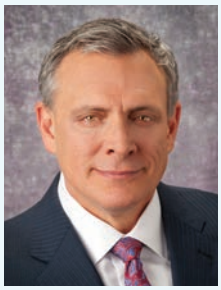
Department News

ATS Distinguished Achievement Award

Steven D. Shapiro, MD has been announced as a recipient of the 2017 Distinguished Achievement Award along with Jack Gauldie, DSc, PhD, Hamilton, Canada, by the American Thoracic Society (ATS).

Dr. Shapiro was recognized on May 21 during the ATS conference in Washington, DC.

The ATS Distinguished Achievement Award is given to individuals who have made outstanding contributions to fighting respiratory disease through research, education, patient care, or advocacy.



Steven D. Shapiro, MD
Executive Vice President, UPMC

Chief Medical and Scientific Officer, UPMC

President, Health Services Division, UPMC

Distinguished Professor of Medicine, University of Pittsburgh School of Medicine

ATS Recognition Award for Scientific Accomplishments

Alison Morris, MD, MS received a 2017 ATS Recognition Award for Scientific Accomplishments on May 22 during the American Thoracic Society Conference in Washington, DC.

The recipients for this award are recognized for either scientific contributions throughout their careers or for major contributions at a particular point in their careers.

Alison Morris, MD, MS
Professor of Medicine, Immunology, and Clinical and Translational Research

Director, Center for Medicine and the Microbiome

Vice Chair for Clinical Research, Department of Medicine

UPMC Chair in Translational Pulmonary and Critical Care Medicine

Dr. Roy Semaan
Bringing Interventional Pulmonology Expertise to UPMC

As the newly appointed director of Interventional Pulmonology at UPMC, Dr. Roy Semaan is implementing the most advanced, cutting-edge techniques to diagnose and treat patients who suffer from an array of lung diseases, such as lung cancer, central airway obstruction, and malignant and non-malignant airway disease.

Dr. Semaan is a former fellow of interventional pulmonology at The Johns Hopkins Hospital, and has also completed fellowships in pulmonology at UPMC and Critical Care Medicine at the National Institutes of Health Clinical Center.

He and his team of interventional pulmonology experts specialize in:

- Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for the staging and diagnosis of lung cancer, as well as electromagnetic navigational assisted endoscopic and transthoracic biopsy of peripheral lung nodules.
- Rigid bronchoscopy for the treatment of malignant and non-malignant central airway obstruction using laser, argon plasma coagulation, cryotherapy, and electrocautery techniques.
- Balloon bronchoplasty and tracheobronchial stenting for central airway obstruction.
- The treatment of pleural disease. His team runs an inpatient and outpatient pleural disease service to diagnose and treat pleural disease using ultrasound guided drainage or placement of pigtail and indwelling pleural catheters.

For more information on Dr. Semaan, or to refer your patients to the Interventional Pulmonology Program at UPMC, call 412-692-2210.

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Clinical and Translational Research in the ICUs of UPMC Presbyterian - Shadyside

Bryan J. McVerry, MD

Acute respiratory distress syndrome (ARDS) represents a life-threatening complication in patients who have one of many systemic inflammatory and primary pulmonary disorders, including sepsis, infectious or aspiration pneumonia, pancreatitis, and trauma, and in patients receiving blood product transfusions. ARDS affects between 100,000 and 200,000 people in the United States each year and leads to death in as many as 35% of patients who experience it. Clinical investigations have demonstrated improved mortality rates when ARDS patients are ventilated with strategies designed to limit cyclic stretch and alveolar over-distension. However, effective adjunctive therapies, targeting the pathogenesis of ARDS, are not currently available.

Currently limiting the design and interpretation of clinical investigations pertaining to ARDS patients is the presence of variable phenotypes of patients with the syndrome. At UPMC, we have developed the Acute Lung Injury Registry and Biospecimen Repository in order to better understand the natural history and varying pathophysiology underlying the development of ARDS and to facilitate development of targeted therapeutics. Patients who participate in this registry will help future patients by providing data for planning and piloting potential therapeutic studies.

The clinical and scientific communities are aggressively searching for effective treatments for ARDS, and physicians in the UPMC Presbyterian Medical ICU are currently enrolling patients in both National Institutes of Health (NIH)- and industry-sponsored clinical trials to that end. As a member of the NIH-sponsored Prevention and Early Treatment of Acute Lung Injury (PETAL) Network (www.petalnet.org), UPMC is recruiting subjects for two large Phase III studies focused on early treatment or prevention of ARDS. In addition, UPMC physicians have partnered with Athersys, Inc. (with NIH support) to conduct an early phase trial focused on the safety and efficacy of bone marrow-derived multipotent adult progenitor cells for the treatment of ARDS. As sepsis is one of the strongest risk factors for the development of ARDS, UPMC physicians are also actively involved in clinical trials targeting the pathogenesis and treatment of sepsis. UPMC physicians have partnered with Bristol-Myers Squibb to study the safety and pharmacology of the biologic agent BMS-936559 in patients with severe sepsis, and will soon be launching a pilot Phase IIa trial studying the anti-inflammatory effects of enteral glucose administration early in the evolution of severe sepsis. Details of the active interventional trials are as follows:

ARDS

- Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) is designed to explore the benefits of early skeletal muscle paralysis for patients with moderate to severe ARDS. (PETAL Network, PI: David Huang, MD, MPH)
- Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) is designed to determine the benefits and safety of early administration of vitamin D for deficient patients at high risk for ARDS and mortality. (PETAL Network, PI: Michael Abesamis, MD)
- A Phase I/II Study to Assess the Safety and Efficacy of MultiStem® Therapy in Subjects with Acute Respiratory Distress Syndrome (MUST-ARDS) is multicenter, randomized, double-blinded, placebo controlled study exploring the safety and potential efficacy of bone marrow-derived human mesenchymal stem cells for the treatment of moderate to severe ARDS. (Athersys, Inc., PI: Bryan McVerry, MD)

Sepsis

- A Phase Ib/IIa, randomized, double-blinded, placebo-controlled, multicenter study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of BMS-936559 in subjects with severe sepsis. (Bristol-Myers Squibb, PI: Florian Mayr, MD)
- Enteral Dextrose as a Therapeutic Agent for Early Sepsis: A Randomized Controlled Clinical Trial is designed to explore the anti-inflammatory properties of dextrose administered through a feeding tube in patients with severe sepsis. (PI: Faraaz Shah, MD and Bryan McVerry, MD)

Finally, UPMC investigators are actively engaged in understanding how best to elicit patients' values in terms of care in the intensive care unit and how to support patients and their families as they struggle with the impact of critical illness and the associated potentially poor prognosis (PI: Douglas White, MD, MAS).

For a complete listing of ongoing ICU studies at UPMC, visit the Multidisciplinary Acute Care Research Organization (MACRO) website at ccm.pitt.edu/macro/actively-recruiting-studies. For more information about each study or for study participant referrals, contact Bryan McVerry (mcverrybj@upmc.edu) or MACRO (Mary Stefanick, RN, BSN, CCRC, stefanickma@upmc.edu).

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