SEPSIS: TREATMENT AT THE SPEED OF LIFE

Innovation and Improvement in the Early Diagnosis, Treatment, and Monitoring of Sepsis at the Michigan Center for Integrative Research in Critical Care
Sepsis may not have the same name recognition as heart attacks or cancer, but it strikes more than 1.7 million Americans every year—15 to 30 percent of which don’t recover.1 One in three patients who die in the hospital die of sepsis. Caused by a body-wide over-reaction to any kind of infection, inflammation and impaired blood flow deprives organs of nutrients and oxygen and leads to multiple organ damage and eventually death.

More people die from sepsis than die from prostate cancer, breast cancer and AIDS combined. Moreover, recent epidemiology studies indicate that the number of people diagnosed with severe sepsis and septic shock is increasing year by year, eclipsing the incidence of stroke, cancer, and myocardial infarction2.

Sepsis treatment is also very expensive, as it often involves a prolonged stay in the intensive care unit and complex therapies with high costs. In fact, the Agency for Healthcare Research and Quality lists sepsis as the most expensive condition treated in U.S. hospitals, costing nearly $24 billion in 2013.3

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To meet the need for next-generation diagnostic tools and therapeutics, the Michigan Center for Integrative Research in Critical Care (MCIRCC) at the University of Michigan has developed a comprehensive approach to enhance the pathophysiologic understanding of sepsis, inflammation and organ failure such as acute respiratory distress syndrome (ARDS), and to develop new technologies for ultra-early diagnosis and therapeutic guidance. These new precision diagnostic and treatment strategies will enable the field to move away from the one-size fits all approaches of the past to more innovative therapies of the future.

At MCIRCC, basic science researchers, clinicians, engineers, data scientists, donors, and entrepreneurs are working together to develop dozens of cutting-edge life-saving treatments and therapies. From point-of-care platforms using biomarkers to immunotherapy, MCIRCC is taking a boundless approach on re-imagining every aspect of sepsis care, ranging from the basic science and definition of the disease to how we diagnose and treat every aspect of the patient and their family.

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1 https://www.cdc.gov/sepsis/datareports/index.html
WHAT IS SEPSIS?

Sepsis is the body’s extreme and abnormal response to an infection. Chemicals released into the blood to fight the infection trigger widespread inflammation that becomes uncontrolled and leads to multiple organ damage. Think of it as “friendly fire” within the body caused by an infection or other insult. Without timely treatment, sepsis has devastating consequences, including tissue damage, organ failure, long hospital stays, recurring complications, and a high death rate.

WHAT IS SEPSIS?

1 in 3 Americans will suffer from sepsis in their lifetime

8 million deaths across the globe per year

1.5 million cases per year in the U.S. with 270,000 deaths

Sepsis is the #1 leading cause of in-hospital deaths

Approximately 30% of patients diagnosed with severe sepsis do not survive

Up to 50% of survivors suffer from post-sepsis syndrome*

In 2014, sepsis was the most expensive in-patient cost in U.S. hospitals, averaging more than $18,000 per hospital stay

With over 1.5 million sepsis hospital stays in 2014 per year, that works out to costs of $27 billion each year

Sepsis Alliance (sepsis.org)

“A Closer Look at Sepsis-Associated Mortality”

“Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals ”
THE MCIRCC SOLUTION
From Bench to Bedside

MCIRCC’s integrative approach to research plays a significant role in developing strategies that enable translational research, which includes promoting entrepreneurship and commercialization.

MCIRCC has a unique innovation and commercialization program designed to create breakthrough therapies and diagnostic tests that contribute to our overall mission of reducing the burden of severe sepsis and septic shock. MCIRCC supports discoveries from the laboratory all the way to drug, device and diagnostic licensing and approval.

**PROPOSAL DEVELOPMENT UNIT**
Consulting and services for multi-disciplinary teams pursuing research awards.

**COMMERCIALIZATION COACHING**
Driving innovations to licensing opportunities by engaging teams with industry partners and seed funding.

**DATA SCIENCE**
Harnessing data to develop models which predict patient outcomes and analyzing data for new technology insight.

**CLINICAL RESEARCH UNIT**
Assisting investigators with patient recruitment, IRB submissions, and data collection/processing.

**SPECIAL EVENTS**
Hosting member events to promote networking, training, education and funding opportunities.

**PRE-CLINICAL CRITICAL CARE LAB**
Generating high-fidelity large animal models of multisystem disease and injury.
The Center for Integrative Research in Critical Care is the innovation hub for more than 200 critical care researchers across the University of Michigan from 7 schools/colleges and 43 departments.

As one of the first comprehensive enterprises devoted to transforming critical care medicine, we foster multidisciplinary collaborations between our members—unifying scientists, clinicians, engineers and industry partners—to accelerate science and deploy cutting-edge solutions that elevate the care, outcomes, and quality of life of the critically ill and injured.

In the last four years, MCIRCC multidisciplinary teams have licensed ten new products, started 5 new companies, and received more than $30 million in funding toward innovative projects in critical care.
PRODUCT DEVELOPMENT PORTFOLIO

**Smart Pipette**
The Smart Pipette is a battery-operated, portable, biomarker analysis microsystem that is wirelessly connected to a smartphone for data transmission and analysis. The data is analyzed and correlated with sepsis severity, treatments, and outcomes to result in timely intervention and to predict sepsis development. The technology is combined with advanced machine learning algorithms allowing for rapid bedside measurement of multiple biomarkers for precision diagnosis and trajectory monitoring of sepsis.

**Nanorod-PCR**
MCIRCC members are developing an assay that utilizes nanotechnology to detect bacteria in whole blood in under two hours without traditional blood cultures. The ability to rapidly detect bacterial DNA signatures will allow physicians to prescribe the “right drug for the right bug” for septic patients. This will also help in reducing the problem of bacterial antibiotic resistance and the development of “superbugs.”

**Vascular Tone Monitoring System (VATMOS)**
Licensed to New Vital Signs, Inc., VATMOS monitors arterial vascular tone which is an important cardiovascular parameter in sepsis treatment but one that currently requires catheters to be placed into the heart to monitor. This unique, wearable sensor is worn on the finger and connects to a portable device or monitor to continually measure the vascular tone and reactivity. The sensor uses algorithms to extract cardiovascular signals in blood vessels responsible for arterial tone. Changes in these signals can predict cardiovascular collapse and how patients will respond to certain medications to control blood pressure.

**Dynamic Respiratory Impedance Volume Evaluation (DRIVE)**
DRIVE utilizes changes in limb blood volume produced by breathing, as measured by changes in impedance, to monitor a patient’s circulating blood volume without the risks of a more invasive method. Licensed by New Vital Signs, Inc., this small, wearable and wireless device provides personalized and continuous diagnostic data that can help guide clinical decision making on providing intravascular fluid treatment for sepsis.

**Microvascular Tissue Oximeter**
Licensed to Pendar Technologies, MCIRCC investigators developed a microvascular oximeter utilizing resonance Raman spectroscopy to non-invasively measure peripheral tissue hemoglobin oxygenation (StO2) as a real-time indicator of reduced tissue oxygen supply from sepsis and septic shock. The technology is portable, allows for point-of-care and continuous monitoring, and replaces a very invasive technique requiring placement of a catheter inside the heart.
Predictive Analytics

Predicting ICU Transfer and Other Unforeseen Events (PICTURE)
PICTURE is a powerful machine learning algorithm based on electronic medical records (EMR). It can predict which patients may develop sepsis as well as if patients will deteriorate and require admission to an intensive care unit.

The Analytic for Hemodynamic Instability (AHI)
AHI is a unique automated computer algorithm that utilizes data from a single lead of a non-invasive electrocardiogram (ECG) signal for analysis and early identification of hemodynamic decline, which is a common complication of sepsis. This non-invasive technology, licensed from MCIRCC by Fifth Eye, allows for intervention well before the development of organ injury.

Blood Vital Sign Platform
This unique blood vital sign platform measures important blood properties such as viscosity, red cell deformability, coagulation, and redox potential (oxidative stress). The combination of these variables may be extremely important in monitoring the health of a patient’s blood which can be severely affected by the inflammation of sepsis. These indicators can help guide the use of anticoagulation medicines, blood transfusion, fluid administration, use of antioxidants, and in understanding the severity of inflammation including oxidative stress. The platform is also envisioned to help guide the development of a new generation of therapeutic interventions.

Non-invasive Central Venous Pressure Monitoring
MCIRCC scientists have developed and patented an impedance-based, non-invasive method to measure central venous pressure (CVP). CVP is the pressure within the right atrium (a chamber of the heart). Monitoring and optimization of CVP can improve heart function and prevent renal failure and other complications associated with sepsis. Measurement of CVP could previously only be measured through invasive procedures, which carry risk and can only be done in special settings.

Therapeutic Vibration Device
MCIRCC is developing a device that delivers specific vibration frequencies to the entire body that increase blood flow to vital organs. The device is easy to apply and increases peripheral organ and brain tissue oxygenation. The device can also cause muscle contraction and increase oxygen consumption as a countermeasure to the myopathy that occurs during prolonged immobilization in the ICU during sepsis. Use of such therapies may reduce the length of stay in the ICU and lead to faster recoveries, helping to avoid the post intensive care syndrome (PICS).

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CURRENT EXAMPLES OF FUNDED RESEARCH

Sepsis Metabolomics:
Metabolomics (the simultaneous measurement of small molecules in a single biological sample) of sepsis is shedding light on the mechanistic underpinnings and metabolic pathway disruption of the disease. Such studies can be used to identify drug-target opportunities. The MCIRCC team of investigators, with funding from the National Institutes of Health, are tracking longitudinal changes in the sepsis blood metabolome by measuring differences in arterial and venous blood and assessing organ-specific changes in metabolism. The metabolic signals of sepsis can also be linked to other systems’ biology domains (e.g., proteomics and genomics) that help define such complex disease states.

The Sepsis Microbiome
The microbiota of the gut and lung are both profoundly altered in sepsis, and these bacterial communities are both correlated with severity of illness and predictive of disease outcomes. MCIRCC investigators, with funding from the National Institutes of Health, have unmasked a crucial relationship between the pathogenesis of sepsis and the trillions of bacteria that inhabit our patients. The microbiome is “the forgotten organ in multi-organ failure” and represents an enormous untapped target for the prevention and treatment of sepsis.

Big Data Analytics of Sepsis
Hospitalized patients with or at risk for sepsis and states of organ inflammation and failure such as Acute Respiratory Distress Syndrome (ARDS) can produce massive amounts of data from monitoring signals, labs, images and other sources. Only a small fraction of this data can be interpreted and used to make critical clinical diagnostic and treatment decisions. With funding from the National Science Foundation and National Institutes of Health, MCIRCC investigators are creating novel computational methods allowing for the ingestion, noise removal, and extraction of valuable data to develop new predictive algorithms to diagnose sepsis and ARDS in real-time as well as events that are associated with a worsening in the patient’s condition.
MCIRCC is focused on leveraging our multidisciplinary model of research innovation with our ability to integrate the University of Michigan’s prestigious reputation, campus-wide talent, and extensive resources to bring university-led critical care innovations to market. Our members span many disciplines across the university, yet have the common goal of improving the lives of critically ill and injured patients and their families.

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**Top Ranked Colleges – U.S. News & World Report**

- **#3** Pharmacy
- **#4** Engineering
- **#5** Public Health
- **#8** Nursing
- **#15** Medical School

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**Research Powerhouse**

- **#1** Research Spending - Public University
- **#10** Medical School NIH Funding
  National Institutes of Health

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**World-Class Health System**

- 3 Hospitals
- Level 1 Trauma & Burn Center
- 10 Critical Care Units
  Including the nation’s first ICU in an Emergency Department
- **#5** - Best Hospitals Honor Roll
  U.S. News & World Report

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With current scattered and insufficient funding sources discouraging high-risk research, enhancing long-term survival for sepsis patients requires solutions that seem almost like science fiction. So we are embarking on a unique partnership model that depends upon private support from donors, investors, and entrepreneurs.

And while the investment is great, the return on the investment is even greater. These funds will enable MCIRCC teams to perform high-risk research, maintain research facilities, engage our members, and enable scientists, engineers, and clinicians to investigate problems and invent the solutions necessary to save lives.

**CASE STUDY: JUST BREATHE - NEW DEVICE DIAGNOSES LUNG DISEASES USING EXHALED BREATH**

Breathalyzers have been used for decades to measure the amount of alcohol on breath, but what if they were able to detect illness? Researchers at the University of Michigan have developed a new point-of-care device that can diagnose life-threatening lung diseases using just a patient’s breath.

Exhaled breath contains hundreds of volatile organic compounds (VOCs) that carry important information about our physiology. Diseases can impact VOC combinations and create unique patterns known as a “breathomic signatures.”

Xudong Fan, PhD, Professor of Biomedical Engineering and Associate Director of the Michigan Center for Integrative Research in Critical Care (MCIRCC), partnered with Kevin Ward, MD, Executive Director of MCIRCC and Professor of Emergency Medicine and Biomedical Engineering, to develop a device that recognizes and analyzes breathomic signatures to help with early and precision diagnosis and to guide therapy.
While the technology, known as gas chromatography, has existed for years, the machines have never been practical for bedside monitoring. Fan and Ward have re-engineered this technology to analyze vapor molecules on a parts-per-billion scale. “We’re able to get high-fidelity results in a much smaller package, and there’s no additional cost to the patient,” said Fan.

Fan and Ward’s micro-gas chromatography device is fully automated and weighs only nine pounds. The device uses an algorithm that can generate diagnostic results in less than twenty minutes, so monitoring takes place in real-time. The device is also useful for monitoring patient trajectory once treatment has begun.

The technology is being developed and tested to help diagnose and track the severity of the Acute Respiratory Distress Syndrome (ARDS). ARDS is the most severe type of lung injury affecting over 200,000 patients/year in the U.S. and resulting in over 75,000 deaths. Sepsis is one of its major causes.

The device is being demonstrated to detect ARDS earlier and to perform better than a clinician in determining if the disease is improving or worsening. Fan and Ward also envision this device improving outcomes for other inflammatory diseases such as pneumonia, sepsis, asthma and others. The team, initially funded by FFMI’s Michigan Translational and Commercialization program, has also received funding from the NIH’s Center for Accelerated Innovations based at the Cleveland Clinic. The data has been so promising—more than 90% accurate—that the team received an NIH R21 exploratory/development grant from the National Institutes of Health to advance the technology and test it in more patients. The team has several pending patents on the technology and is starting a new company.
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