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August 31, 2018

Jon Lorsch, M.D.
Director
National Institute of General Medical Sciences
45 Center Drive MSC 6200
Bethesda, MD 20892-6200
RE: NOT-GM-18-039

Dear Dr. Lorsch:

On behalf of the American Thoracic Society (ATS), thank you for the opportunity to provide comments on the NIGMS's RFI, NOT-GM-18-039, on sepsis research. The ATS is pleased that the Institute plans to accelerate sepsis research. We look forward to continued engagement with the Institute on the development of this framework. We have the following comments:

1. **Current barriers that hinder advancement of research related to sepsis**
   - **Funding sources**
     The current mechanisms through which sepsis research is primarily supported at NIH are divided between NIGMS and the National Heart, Lung and Blood Institute (NHLBI), which hinders the establishment of an integrated sepsis research agenda. The ATS recommends that the NIGMS and NHLBI, with appropriate input from stakeholders including the ATS, develop a coordinated and collaborative strategy to produce a unified research agenda for basic, clinical and translational sepsis research to improve our knowledge, detection, treatment and prevention of the disease.

   - **Availability of sepsis cohort data**
     There is a lack of well-defined existing sepsis cohorts, particularly availability of biological samples and/or long-term follow-up data to allow for detailed assessment of risk for sub-groups of sepsis patients, mechanisms of disease, and associated outcomes. The ATS recommends that the Institute promote and support the creation and maintenance of well-defined sepsis cohorts.

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- **Understanding the timing of sepsis**
  A key barrier to advancing sepsis research is poor understanding of the timing of when patients present to the emergency room, are admitted to hospitals and/or admitted to intensive care units. The potential variability in onset of sepsis and the lack of knowledge of this timing are areas that warrant better understanding to ensure homogenous cohorts and assessments.

- **Sepsis in vulnerable populations and underrepresented minorities**
  Other key areas of need within sepsis research are for more knowledge about sepsis stratification in the different genders and in under-represented minorities and special populations including the elderly, immune-compromised individuals, pregnant women and people of color.
  There is currently a dearth of data regarding sepsis in these populations. For example, sepsis is different in populations such as young IV drug users, frail elderly patients and pregnant women. There is also a lack of knowledge about the endo-types of different patient populations relative to the severity of sepsis. The ATS recommends that the Institute expand these areas of study.

2. Gaps in currently supported research areas and approaches

- **Funding for large clinical trials**
  There is a lack of funding mechanisms across the NIH to support key types of sepsis research, such as health services research (NIGMS currently does not support this area of study). The NHLBI generally focuses on supporting sepsis research in the context of lung disease (e.g. ARDS or acute respiratory failure). The ATS recommends that the NIGMS provide funding opportunities for all types of sepsis research, including pilot and definitive clinical trials, outcomes, health services, translational, and basic science, and develop cross-institute opportunities to support health services research on sepsis.

- **Inter-disciplinary investigator initiatives**
  Another critical need within sepsis research is for more interdisciplinary investigational initiatives. The ATS recommends that the NIGMS develop and support opportunities to engage diverse healthcare professionals, including (but not limited to) nurses, dieticians, physical therapists, respiratory care practitioners, statisticians, engineers, outcome researchers and emergency medical technicians in sepsis research projects. Engaging diverse healthcare professionals will promote the sharing of ideas and allow these professionals to bring their expertise to sepsis research. Engagement and education of other health professionals in these ways could help promote earlier identification of sepsis and potentially lead to better patient outcomes.

- **Biomarkers for presence and severity of sepsis**
  Early identification and better understanding of the diversity of the patient population with sepsis and septic shock (for example, utilizing point of care biomarkers) may expedite treatment, improve anti-microbial utilization decision-making, provide guidance about the aggressiveness of care, and result in better patient outcomes. The ATS recommends the Institute supports further research to identify sepsis biomarkers and other potential measures of the presence and severity of sepsis.

- **Genetic predisposition to sepsis**
  There remains a need for better understanding of genetic predisposition to sepsis. The ATS recommends the Institute supports more study in this area.

- **Healthcare practice mandates lacking proven effectiveness**
  Finally, the Centers for Medicare and Medicaid Services (CMS) mandate that clinicians treating patients with sepsis perform and document particular clinical practices for reimbursement. However, some of these mandates are not uniformly supported by robust research demonstrating their effectiveness. An example is the utilization of the
  serial lactate measurement in sepsis, which is required by CMS but has not been proven to improve patient outcomes. The ATS recommends the Institute collaborates with agencies such as the Agency for Health Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI) to support patient-centered outcomes research of sepsis clinical protocols.

3. Development of more diverse animal models

The use of research organisms other than the standard mouse model would benefit sepsis-related research. Critical care researchers should be able to utilize different animal models for different organ-system based injury study. We believe there is potential to use large animal models to examine organ perfusion in sepsis, which cannot be easily assessed with murine models. Another key area of need is for an animal model for pneumonia-associated sepsis. The ATS recommends that the Institute develop and support the use of alternative model organisms to evaluate sepsis.

4. Appropriate mix of fundamental and clinical sepsis research

The ATS believes that combining fundamental and clinical sepsis research is crucial for advancement of this field, but the opportunity to engage both of these areas simultaneously is challenging for several reasons including: 1) lack of trained and experienced translational researchers who can straddle both the clinical and basic science areas, 2) lack of opportunity for collaboration between clinical researchers and basic science researchers, 3) logistic difficulty of obtaining human samples during large human clinical study, and 4) lack of infrastructure to process, store, assay, and ship human samples at clinical research sites. Overcoming these challenges requires specific emphasis on finding and supporting solutions to each barrier.

5. The need, if any, for shared resources

Given the complexity of sepsis research and the need for almost all human studies to include multiple clinical enrolling centers, developing the tools and infrastructure for large-scale shared resources is key to improving our understanding of pathogenesis, recovery, and treatment of sepsis. The ATS has thus identified the following needs for shared resources:

1. Trans-NIH institute biobanks for sepsis research
2. Shared large animal models, due to their high cost
3. Greater use of human ex-vivo perfused organ models using organs from declined transplant donors
4. Mechanisms to permit sepsis and other researchers to communicate with one another for the purpose of utilizing available animal organs for sepsis research

The ATS appreciates the opportunity to comment.

Sincerely,

Polly E. Parsons, M.D.
President
American Thoracic Society