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SCIENTIFIC PRIORITIES AND STRATEGIC PLANNING FOR RESUSCITATION RESEARCH AND LIFE SAVING THERAPY FOLLOWING TRAUMATIC INJURY: Report of the PULSE Trauma Work Group

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ABSTRACT—Traumatic injury and its sequelae remains a major, unrecognized, public health problem in North America. It is the principle cause of death in patients aged 1-44 and the overall leading cause of life years lost in the United States. Recognizing this the National Heart, Lung and Blood Institute (NHLBI), in conjunction with other federal agencies, organized a conference in June 2000 to discuss the basic and clinical research projects that could lead to improved outcomes following cardiopulmonary or post-injury resuscitation. The Post Resuscitative and Initial Utility of Life Saving Efforts (PULSE) Workshop resulted and eight workgroups were established to focus on various aspects including organ systems, pharmacology, epidemiology, and trauma. The Trauma Work group recommendations are presented in this manuscript. Despite the recognition of improved survival and outcome through advancements in trauma systems and trauma care, the National Institutes of Health (NIH) support ratio for trauma research is only 0.10 compared to 1.65 for cancer research and a remarkable support ratio of 3.51 for AIDS and HIV infection research. The successful federal HIV research program has significantly decreased the morbidity and mortality over the last ten years at a cost of 1.4 billion dollars per year. A coordinated trauma research program should aim to replicate the success achieved by such programs; however, a centralized federal "home" for trauma research does not exist. Consequently, the existing limited research support is derived from NIH institutes in addition to other federal and state agencies. This report serves to describe some of the obstacles and to outline various strategies and priorities for basic science, clinical and translational trauma resuscitation research.

KEYWORDS—Funding, clinical care, research strategies, animals models, technologies, system organization, organ systems

INTRODUCTION

The NHLBI, in conjunction with other federal agencies, assembled a conference of leaders in the various fields of resuscitation. The June 2000 conference sought to discuss the basic science and clinical research needs with a goal of improved outcomes following cardiopulmonary or post-traumatic injury resuscitation. The outcome of the (Post Resuscitative and Initial Utility of Life Saving Efforts) PULSE conference was the development of eight workgroups focusing on various aspects including organ systems, pharmacology, epidemiology, as well as trauma (1). The detailed recommendations of each workgroup are published separately in addition to a combined publication (2). The Trauma work group consisted of a wide variety of participants ranging from basic scientists to clinical investigators in surgery, neurosurgery, anesthesia, critical care, and emergency medicine (see acknowledgments) and the recommendations are presented in this report.

STATEMENT OF THE PROBLEM

Traumatic injury is a major, largely unrecognized public health problem in North America that cuts across age, race, gender, and economic boundaries. Accounting for 37 million emergency department visits, 2.6 million hospital admissions, and 150,000 deaths (3); each year trauma kills three times the number of Americans killed during the Vietnam conflict. While injury remains the leading cause of death in the population between ages 1 and 44 and one of the leading causes of death in those over age 65, it is also sobering to note that more children die from trauma than from any other cause (4). The resulting loss of productive life years exceeds that of any other disease, with societal costs (estimated by the National Safety Council) of $260 billion dollars annually. By the year 2020, injury will equal or surpass communicable diseases as the number one worldwide cause of disability-adjusted life years lost (5).

Despite these alarming facts and the recognition that trauma systems and trauma care can significantly improve survival and function, funding for research is woefully inadequate. For example, when trauma funding is placed within the context of years of potential life lost (millions of dollars per years of potential life lost per 100,000 population), the NIH support ratio for HIV is 3.51, for cancer 1.65, and for trauma 0.10 (6). The total 1996 NIH budget allocation for traumatic injury and research was $194.4 million; however, allocations for the treatment and research of cancer were $2.57 billion for the same year (5).

The extraordinary success of the federal HIV research program has resulted in a significant decline in the morbidity and mortality from this disease over the last 10 years at a cost of $1.4 billion dollars a year. A successful trauma research program should duplicate this approach. Several obstacles, however, have impeded the development of a cohesive program with a central scientific agenda and optimal use of resources. First, no centralized federal "home" exists for trauma research, thus, current support depends on several NIH institutes (National Institutes of General Medical Sciences, National Institute of Neurological Disorders and Stroke, National Institute of Child Health and Human Development, NHLBI), the Departments of Transportation at the federal and state levels, the Centers for Disease Control and Prevention, the Agency for Healthcare Research

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and Quality (AHRQ), the Department of Defense, and many scattered state and local Departments of Health. Second, injury prevention and resuscitation research is inhibited by the pervasive public misperception that, on the one hand, injuries that happen to individuals are not preventable, and on the other hand, accidents that happen to other people are somehow their own fault. Another major obstacle is the inability to obtain informed consent rapidly enough to conduct needed research in the emergency setting. Finally, large animal models are required to answer certain crucial questions about trauma management, but vocal opposition to the use of animal models has impeded these investigations.

ANALYSIS OF DEATHS SUGGESTS RESEARCH APPROACHES

The pattern of deaths following injury is of particular note. Forty percent of the 150,000 patients who die annually from trauma do so before reaching the hospital and nearly 80% of all trauma deaths occur within 48 hours of injury. Most of these deaths result from massive hemorrhage and central nervous system (CNS) injury. Improving outcomes in these patients will require prevention that is more effective, new methods of hemorrhage control, and new approaches to monitoring, intervention, and resuscitation.

The remaining (late) deaths occur in patients with a broad spectrum of injuries. Risk factors contributing to mortality include varying degrees of suboptimal perfusion, inadequate oxygen and substrate delivery, imbalanced neurovascular and inflammatory responses, and other factors that confer an increased risk for ischemia/reperfusion insult, which, in turn, may lead to early multi-organ dysfunction. In general, we as medical practitioners and scientists are more successful in restoring normal anatomy than in understanding, recognizing, and treating subtle physiologic derangements. Significantly increased survival and decreased disability in this group of patients will require advanced technology, application of novel research, and treatment strategies developed through coordinated multi-disciplinary resuscitation research.

THE OPPORTUNITY FOR INCREASED MULTIDISCIPLINARY RESEARCH

Trauma is a complex disease that involves direct mechanical injury to tissues as well as systemic disturbances of the entire organism. Thus, the traditional research and therapeutic approach applied to delineating specific cellular and tissue pathology must be placed in the broader perspective of the impact of these perturbations on all organs and systems, e.g., cardiovascular, pulmonary, renal, gastrointestinal, endocrine, coagulation, neurologic, and inflammatory systems. System-based approaches are necessary to translate laboratory-based insights into clinically appropriate therapeutic resuscitation strategies.

Patients experiencing sudden cardiopulmonary arrest following a myocardial event may require different therapeutic approaches than patients with impending exsanguinating arrest following traumatic injury. However, the shared challenge of multi-organ ischemia/reperfusion, regardless of etiology, provides fertile ground for the exchange and development of scientific collaboration in basic mechanisms and translational clinical research. We believe this common challenge can be more effectively addressed through the PULSE multi-disciplinary resuscitation research initiative (1, 2).

STRATEGIES AND PRIORITIES FOR TRAUMA RESUSCITATION RESEARCH

As an integral part of the PULSE initiative, we recommend simultaneous pursuit of research efforts in the areas listed below. The body of currently existing basic knowledge in many areas calls for immediate initiation of clinical studies at the same time that new hypotheses are being explored in the laboratory. For example, significant questions have been raised regarding long-held beliefs about the timing, amount, and type of resuscitation for patients in hemorrhagic shock. Clinical studies addressing these issues can be carried out at the same time as basic studies designed to develop improved resuscitative fluids.

Formation of an infrastructure

A well-defined and organized infrastructure is needed to facilitate transfer of research findings from the bench to the bedside. In addition, laboratory studies encompassing the spectrum from highly focused questions to complex systems interactions need to be appropriately guided. This infrastructure should be cohesive to permit efficient resource utilization and to allow prompt clinical application of scientific findings.

Clinical and translational studies of trauma resuscitation

Formation of a clinically oriented, multi-institutional, multi-disciplinary, trauma resuscitation research consortium. The application of research insights from a wide variety of fields to the treatment of trauma patients will require an integrated, systematic approach to clinical research. This integrated approach to research could be realized by the use of a specialized trauma clinical research consortium. Centers would be selected to augment targeted areas of interest in trauma research. For large multi-center trials, centers of excellence could be organized into national clinical consortiums. Thus, developments in diverse areas, from pharmacogenomics to cardiovascular support devices, could be thoroughly evaluated and any effctive therapy rapidly and rigorously tested.

Development of an improved and coordinated trauma research registry. Trauma is an umbrella term describing a multitude of mechanisms of injury with a variety of corresponding physiological responses that influence the clinical course, required interventions, and outcome. The Trauma Registry of the American College of Surgeons (TRACS) provides a much needed resource for trauma research; however, certain considerations are worthwhile. Although there are currently multiple types of pre-hospital and in-hospital trauma data registries, such registries are not uniform and cannot be easily or reliably merged. For example, the Crash Outcomes Data Evaluation System (CODES) merges clinical data with motor vehicle accident information, but there are only 25 states participating in this program. In addition, a uniform case definition is needed so data are reliably comparable between databases. A unified, coordinated, but comprehensive effort will substantially improve the study of trauma pathophysiology as well as the efficiencies and reproducibility of clinical trials.

Development of animal models. Given the complex dynamics of system as well as systemic responses to traumatic injury, efficient clinical application of laboratory findings requires the use of appropriate animal models. Several of the features that should be considered in developing resuscitation protocols and fluids include: a) mechanistic differences in the specific etiology of the traumatic insult, and b) host variables with respect to age, gender, underlying disease, the influence of alcohol and/or drugs and genotype (as far as some potentially critical predisposing genes are concerned). Intact small and large animal models allow for the standardization of insults, evaluation of multiple systems, complete biological interrogation, and exploration of the full therapeutic potential as well as the limitation of interventions. Comprehensive animal studies must be conducted prior to the institution of a clinical trial for trauma resuscitation.

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Informed consent. Importantly, the critical issue of informed consent in trauma resuscitation research needs to be addressed. In order to conduct any pre-hospital or emergency therapeutic trial, an emergency consent or waiver of consent is required for research with a minimal incremental risk. Existing informed consent regulations require obtaining explicit permission from either the patient or legal surrogate (e.g., spouse) before enrollment into a clinical trial. Due to the severity of their injuries, traumatized patients are usually unable to provide informed consent. As trauma is an emergency condition, there is often insufficient time to locate a surrogate. Thus, in order to conduct incremental minimal risk clinical research to ameliorate the highly morbid disease of severe trauma, a new provision for a waived, implicit or implied consent is needed so that patients can be enrolled in trauma resuscitation studies.

Initial emphasis should be focused on:

Optimal fluid resuscitation: Hemorrhagic shock after injury results from reduced circulating fluid volume. Early transport for trauma patients by emergency medical services (EMS), including field intravenous fluid resuscitation, has contributed to a steady reduction in early mortality; however the contribution of intravenous fluid resuscitation to this success is not clear. Patients with seemingly adequate cardiovascular resuscitation still die of the multiple organ failure (MOF) syndrome, the leading cause of delayed death after trauma. Recent research has suggested that MOF is associated with hyperinflammation, coagulation dysfunction, and impaired metabolism.

Even the choice of resuscitation fluid has been challenged based on recent research. Widely used stored human blood products generate pro-inflammatory mediators, which contribute to hyperinflammation and possibly to MOF. Hemoglobin-based blood substitutes can increase oxygen carrying capacity and improve arterial blood pressure during resuscitation; yet, nitric oxide scavenging by these agents can shunt blood from microcirculatory beds and lead to organ ischemia, dysfunction, and death. Similarly, hypertonic saline resuscitation studies have focused upon restoration of the hemodynamic state instead of incorporating recent insights of hypertonic saline's effects on immunomodulation. Thus, further research is needed to determine the optimal timing, duration, amount, and type of intravenous fluid resuscitation after trauma.

Hemorrhage control: Certain patients have increased blood loss if aggressive fluid resuscitation is utilized prior to definitive control of hemorrhage since the increased pressure with fluid resuscitation increases exsanguination. This suggests that fluid resuscitation strategies must be coupled to bleeding control. New insights into local and systemic modulation of the coagulation system after trauma and novel techniques to control bleeding are required.

Ventilatory and oxygenation support: Traditional methodologies for supporting oxygenation and ventilation (100% O_2, positive pressure ventilation and rapid respiratory rate) may have significant detrimental effects, in terms of both cardiac output and microcirculatory effects in the moribund trauma patient. Alternative respiratory methodologies, such as those that sustain or enhance intravascular circulatory flow while still helping to oxygenate, are urgently needed.

Management of primary and secondary CNS injuries: Traumatic brain injury (TBI) is the leading cause of death and disability in both civilian and military patients. Traumatic spinal cord injury (SCI) also occurs frequently, with close to 10,000 new cases reported each year. In addition to isolated TBI and SCI, injury to the CNS can result from secondary complications of traumatic injury elsewhere, e.g., spinal cord ischemia due to hemorrhagic shock. Combined traumatic injury that includes the CNS has been shown to be particularly lethal. It is not clear whether this is due to a negative synergistic effect of the injuries or to exacerbation of TBI due to clinical interventions, e.g., worsening intracranial hypertension with high-volume fluid resuscitation. Other important CNS-related trauma conditions are secondary TBI and spinal column injuries due to episodes of hypotension.

Two areas of trauma research that need additional emphasis are penetrating TBI and spinal cord injury. Penetrating TBI is a common injury, particularly in major U.S. metropolitan areas. However, largely due to negative social and political considerations concerning animal models, research has stopped on this important disease state.

Spinal column injury is perhaps the most common condition among traumatic CNS injuries. Although these injuries may not necessarily involve the CNS directly, peripheral nerves and roots can be affected and the instability of the spinal column places the spinal cord at risk. The impact of this disease on productivity in the US and its cost to society is high. Thus, a meaningful research initiative is needed.

Evaluation tools that also provide an accurate prognosis for the injury are needed to improve patient care. Studies are needed on neuropsychological and neurobehavioral outcomes, with treatment strategies focused on improving both. Research is needed in chronic rehabilitation therapy as well as family intervention and patient/family coping.

Basic Pathophysiology

Microcirculatory dysfunction. Microcirculatory dysfunction after trauma contributes directly to cell injury since it deprives the tissue/cells of O_2 and the nutrients needed for the maintenance of tissue functions. The pathways that mediate microvascular dysfunction are the focus of active investigations. In addition, the search for the ideal resuscitation fluid and resuscitation modalities for improving the microcirculation is proceeding but, certainly, is far from complete.

Endothelial cells. Recent evidence supports a critical role of the endothelium as a tissue that not only separates the blood from other organs and tissues, but also plays a critical role in the communication between leukocytes and other organs including coagulation factors. Furthermore, trauma and subsequent resuscitation activate endothelial cells to recruit neutrophils from the circulation. Once the neutrophils adhere to the endothelium, cytotoxic proteases and oxygen-derived free radicals are released, which are responsible for the end-organ damage. Mechanisms involved in endothelial cell activation are becoming increasingly understood. For example, a recent randomized trial demonstrated that recombinant human activated protein C decreases mortality in patients with septic shock (7). Since both trauma and septic shock present similar pathophysiology, such novel interventions are particularly promising in trauma patients. Furthermore, correlation of circulating mediators with endothelial cell function in different compartments of the body will be particularly important.

Ischemia/reperfusion. Both the absence (ischemia) and the restoration (reperfusion) of blood flow cause damage to various cell structures and functions, including endothelial cell function.

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Cellular damage in the vascular compartment alters the rheological properties leading to impairment of the microcirculation and the initiation of inflammatory reactions. A complex cascade of events, particularly a marked decrease in energy status and alteration in homeostasis, occurs following ischemia-reperfusion. Thus, the future of fluid resuscitation lies in the utilization of new technologies that will improve monitoring and promote restoration of tissue or organ function following trauma. Resuscitation fluids should restore hemodynamic stability without impairing the coagulation system, prevent ischemia-reperfusion injury, regulate pro- and anti-inflammatory responses, restore microcirculation, provide nutrients, and maintain organ and tissue metabolism. In addition, therapeutic adjuncts that show promising effects in the restoration of tissue microcirculation and endothelial cell, immune, coagulation, cardiovascular, and pulmonary functions also appear to be useful in preventing microbial infection and subsequent sepsis. Furthermore, gender and age are important factors in trauma that should not be overlooked.

Functional genomics. Recent advances in technology make it possible to determine not only genome-wide changes in transcription and translation induced by trauma, but also genotypic variations that alter outcome. The fields of functional genomics and pharmacogenomics will provide an opportunity to model and then test novel approaches to understand adaptations to trauma. The emphasis is placed on functional genomics, as any genomic-based approach will be understood in the context of the other entities that determine organism complexity.

Physiologic system interactions. Injury disrupts the function of organs and tissues. Coordinated function of these tissues is essential for homeostasis. Thus, understanding the adaptive response requires integration of knowledge at the molecular, cellular, tissue, and organ levels. Extracting information from the enormous data sets produced by these highly parallel, genome-wide investigations requires the application of novel analytical tools that query complex adaptive systems.

Technologies and Devices

Anatomic and physiologic evaluation of injury. Field diagnosis will be enhanced by the capacity to identify anatomic injury by utilizing noninvasive, accurate, portable devices for assessment, i.e., brain edema and/or hemorrhage or intracavitary hemorrhage. Noninvasive biosensors should be developed to record traditional vital signs and quantify circulating blood volume, adequacy of cardiac function, and tissue metabolism during out-of-hospital resuscitation of trauma victims.

Systems for reliable pre-hospital data analysis. Integration and analysis of real time physiologic and metabolic data across the pre-hospital and hospital continuum is a particularly promising means of improving the effectiveness and efficiency of the care for trauma patients. This same system will allow accurate documentation of pre-hospital interventions and the development of effective decision assisting devices.

Therapeutic interventions and treatment strategies. The development of innovative methods of achieving rapid vascular access, hemorrhage control, cerebral protection, optimal methods of resuscitation and novel metabolic manipulation are required to decrease morbidity and mortality. Methods of hemorrhage control will include local manual measures such as high-density bandages, intracavitary agents, or intravascular clotting factors. Cerebral protection will entail new methods of decreasing edema and hemorrhage. New methods of resuscitation may include using different intravenous fluids and/or hemoglobin substitutes and new endpoints of therapy. Metabolic manipulations may include utilizing the beneficial effects of hypothermia and/or suspended animation.

Simulation. The use of sophisticated human patient simulators for training and testing will allow a reproducible learning environment with consistent standards. Integration of the virtual skill stations with realistic haptics will further the usefulness of successive generations of human simulation. Furthermore, integration of the physiologic data accumulated in the field will improve the realism of the simulated environment.

Telemedicine. Use of advanced communication technology currently allows reliable verbal links between advanced centers and the field for acute trauma care. Future possibilities include teaching, monitoring, and interpretation of advanced diagnostic techniques and therapeutic interventions utilizing high bandwidth audio and/or video technology. Technology and devices will be utilized for the continuous pre-hospital collection of various physiologic data. These data will be analyzed and integrated into decision assisting devices and utilized to document the requirement and effect of new methods of rapid vascular access, hemorrhage control, cerebral protection, optimal methods of resuscitation, and novel metabolic manipulation. Simulation and communication technology will be used to document teaching, training, and appropriate interventions.

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