Controversy Swirls Around Early Goal-Directed Therapy in Sepsis: Pioneer Defends Ground-Breaking Approach to Deadly Disease

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Plans to re-examine a research finding via a much larger set of clinical trials, a common event in medical research, have provoked an uncommon result: an unusually public airing in the mainstream media of allegations, financial questions and wounded professional pride.

The research finding at the center of the dispute is early goal-directed therapy for sepsis, formulated 7 years ago by Emanuel P. Rivers, MD, MPH, vice chairman and director of research in emergency medicine at Henry Ford Hospital in Detroit, MI. Dr. Rivers, who trained in critical care, emergency and internal medicine, proposed applying the “golden hour” to severe sepsis and septic shock.

His protocol identified patients and began treating them in the emergency department (ED), before they were admitted to intensive care. It deployed a bundle of conventional measures—early recognition of patients with a high risk of death using blood lactate levels or hypotension and giving antibiotics, fluid therapy titrated to central venous pressure, vasopressors if required to maintain blood pressure, hemoglobin concentration above 10 mg/dl using transfusions if required, and maintaining central venous blood oxygen saturation above 70% using medication (Inotropes) to improve perfusion.

And it had dramatic results. Dr. Rivers’ protocol cut the mortality rate in the 130 patients who received it to 30.5%, compared to 46.5% among the 133 patients treated with the hospital’s standard care—a drop in deaths so striking that the study’s data safety monitoring board decided to end it early. That seemed a significant advance for a disease that affects 750,000 Americans each year and costs from $16.7 to $24 billion and that had had an intractable mortality rate for 3 decades.

Rivers’ protocol was adopted by the Surviving Sepsis Campaign, which is endorsed by the American College of Emergency Physicians and the Society of Critical Care Medicine, and is recommended by the Institute for Healthcare Improvement.

Early goal-directed therapy drew some criticism from the start, and EDs were slow to adopt it: 3 years after it was published, a survey of 30 academic medical center EDs, found only 2 using the protocol. (There is no registry of EDs that use early goal-directed therapy, but it has been adopted by several large health systems, and a July 2008 paper surveyed 40 hospitals now using it.)

Departments that have adopted it are enthusiastic. In a 2006 article in Chest, describing a yearlong trial at Cooper University Hospital in Camden, NJ, Stephen Trzeciak, MD, MPH, declared that early goal-directed therapy “could reliably be achieved in real-world clinical practice.” And later that year, authors from 9 institutions, including Trzeciak and Rivers, reported the outcomes of implementing early goal-directed therapy in 12 institutions other than Henry Ford; all 12 had comparable declines in sepsis mortality rates.

Over all, at least 25 papers supporting the Rivers protocol have been published since 2001, according to the PubMed database. A recent meta-analysis of 9 studies covering 1,001 patients confirmed that the protocol reduces sepsis deaths.

But early goal-directed therapy has still faced questions. They range from the relatively small size of Rivers’ original study, the fact that it was conducted at a single institution, and the reality that it remains the only randomized clinical trial of early goal-directed therapy; to the necessity of the specific monitoring catheter; to whether the protocol is reproducible in thinly staffed community hospitals and very crowded urban EDs.

In response, the National Institutes of General Medical Sciences, part of the National Institutes of Health, announced in late 2006 that it would grant $8.4 million over 5 years to test the Rivers protocol in a much larger randomized trial. The study, called ProCESS (Protocolized Volume 52, No. 6 : December 2008 Annals of Emergency Medicine 651
Care for Early Septic Shock), plans to enroll 1,935 patients at 24 institutions and will be directed by investigators at University of Pittsburgh Medical Center.14

So far, so normal: a creative researcher produces a path-breaking finding, and after a period of exploration and debate, the finding is re-examined for reproducibility. “It is a basic tenet of scientific investigation that you should be able to replicate a work in a different and bigger setting to make sure it is truly helpful,” said Donald Yealy, MD, of the University of Pittsburgh, one of the ProCESS trial’s principal investigators. (Yealy is a deputy editor of Annals but was not involved in the preparation of this story.)

DR. RIVERS RESPONDS

But the next step in the saga of early goal-directed therapy has been somewhat outside the norm. On August 14, the Wall Street Journal ran a front-page article that questioned both Rivers’ analysis and his ethics.15

Citing unnamed “hospital statisticians” and “people familiar with the events,” the article charged that 25 patients were randomized into the trial and then removed before the final analysis; when the data was recomputed with all 288 patients, it said, the 16 percentage-point difference in mortality rates between the groups became not statistically significant. Further, it said that “some doctors who contend that hospitals may be adopting the new therapy prematurely point to financial and patent issues” and raised questions about payments made to Rivers by Edwards Lifesciences, maker of the central venous catheter used in early goal-directed therapy, after the study was published in 2001.

Most strikingly, the article attributed a tone of anger and disappointment to Rivers, saying that he “has called his critics in Pittsburgh ‘the Pittsburgh pirates’” and that in an email to an unnamed acquaintance, he “said some see criticism of his therapy as a ‘thinly veiled academic lynching.’” Rivers ascribed the phrasing to unnamed colleagues.

In response to the Wall Street Journal article, the Henry Ford Health System issued a point-by-point rebuttal16 stating that patients were not taken out of the trial after being randomized, that the mortality rate would not change if the patients were hypothetically added back in, nor that biostatisticians involved with the study disagreed with the analysis. (The original paper gives the numbers this way: “We evaluated 288 patients; 8.7 percent were excluded or did not consent to participate. The 263 enrolled were randomly assigned to undergo either standard therapy or early goal-directed therapy.”)

The rebuttal also said that funds received by Rivers were for research-related costs and speech honoraria after the study was published, and that to avoid conflicts of interest he declined both patent rights for modifications to the Edwards catheter and more than $160,000 in royalty payments.

In a separate statement,17 the Henry Ford Health System Board of Trustees and Directors said it “supports Dr. Rivers and the pioneering research that he has conducted, which has literally saved thousands of lives around the world.” The rebuttal also stated that the early goal-directed therapy was not funded by industry funds. All funds were received after the study and over 7 years (2001 to 2008) and in compliance with the institutional policy of disclosure.

The American College of Emergency Physicians convened a critical care working group in the wake of the Wall Street Journal article and was to announce in October that it continues “enthusiastically” to support the Surviving Sepsis Campaign and thus early goal-directed therapy, though it noted some elements of the protocol “remain somewhat controversial.” The statement cited the continuous monitoring catheter, blood transfusions, “stress dose” steroids and “tight” glycemic control as the controversial elements.

In an interview after the Wall Street Journal article was published, Rivers expressed frustration with other investigators’ desire to recapitulate his research after so many other publications have supported it, and concern that those enrolled in the coming trial will not receive optimal treatment.

“Because this therapy is so basic, and has been recommended for so many years by intensivists, it is almost a foregone conclusion that this kind of treatment should be done. Yet some feel there should be some science applied to it to prove it,” he said. “Nobody has proven stoplights change outcomes, yet will anybody do a study where they will take stoplights from intersections and prove it? . . . There are many centers and people who feel this is the right thing to do for patients. It is almost unethical to randomize someone (away from it).”

Dr. Rivers voiced regret—that the initial, ground-breaking accomplishment by the staff and community of Henry Ford, a large urban inner city hospital in a very poor area, will be lost in the controversy.

“There was no money coming from anywhere,” he said, citing a long list of funding sources that turned away his grant proposals. “It was a grassroots effort by everybody from the nurses to the medical students and even high school students. We used a little bit of everybody. We were quite proud of it.”

PATIENT POPULATIONS

Ironically, it is precisely because the original trial took place at Henry Ford that some researchers want to revisit it. They wonder whether the baseline mortality rate of 46.5%—higher than most recorded elsewhere in the literature—may have been distorted by the
poor health status and high chronic disease incidence in metro Detroit’s largely poor, largely minority population.

“The patient population they have at Henry Ford is not reflective of the general US population,” said Edward Panacek, MD, MPH, professor of emergency medicine and director of the office of clinical trials at University of California, Davis. Dr. Panacek was a member of the data safety monitoring board on the original Rivers study, and is an investigator in the ProCESS trial. “And their aggressiveness, and the critical care orientation in their emergency department, is pretty unique. . . . It could be they are capable of doing many things better with critically ill patients than the average emergency department. Or it could be this therapy shows greater benefits in the type of population they treat.”

Rivers, citing 2 reviews he authored,18,19 rebutted that similar mortality gains have been achieved in populations with similar disease burdens and mortality rates.

That high baseline mortality rate is one of the questions the ProCESS investigators and others want to explore. Two large foreign trials of early goal-directed therapy are beginning roughly simultaneously: the Australia (and New Zealand) Resuscitation in Sepsis Evaluation (ARISE), and the British Protocollised Management in Sepsis (ProMISE) Preliminary research for ARISE, drawing on a shared Australia and New Zealand database of more than 600,000 ICU admissions, found a mortality rate from sepsis of 34% in 1997, around the time the Rivers study began enrolling patients; by 2005, without any early goal-directed therapy being administered in the 2 countries, it had declined to 21%, according to Sandra L. Peake, BM MS, BSc (Hons), of the Queen Elizabeth Hospital in Adelaide, who is chair of the ARISE management committee.

The ProCESS protocol14 calls for 3 arms: standard therapy for severe sepsis, in whatever manner it is practiced at the participating institutions; the Rivers early goal-directed therapy protocol, using the Edwards catheter to deliver continuous monitoring of venous pressure and oxygen saturation; and a middle path that will not use the catheter but will use the fluid boluses, vasopressors and packed red blood cells used in early goal-directed therapy, though not necessarily as rapidly.

The point of the middle path (called “protocollized standard care” in the trial design) is to ascertain whether deploying the entire early goal-directed therapy bundle is necessary in order to get the results that the Rivers trial achieved. In practical terms, that arm will address objections raised in surveys of EDs, that early goal-directed therapy requires too much physician time for placing central lines’ as well as too much staff time and attention, not only for active monitoring but for keeping track of the monitors and cables themselves as patients are transferred.

More broadly, though, it will explore the question of how a complex intervention can be evaluated for efficacy and transferred to clinical practice, given that classical clinical trial design is intended to evaluate only one drug, device or action at a time.

“In early goal-directed sepsis care, the intervention studied is the total protocol and the team,” investigators from the ProCESS, ARISE and ProMISE trials warned in an April paper. “It may not be possible to determine which particular part of the intervention is the primary reason for any observed change in mortality.”

“I personally believe early goal-directed therapy made a difference” to patients’ survival in the original Rivers study, Dr. Panacek said. “However, what is less clear is which parts of early goal-directed therapy made a difference. Some of the parts have to be more important than others.”

The ARISE trial has only 2 arms — early goal-directed therapy and standard care — because with a grant of $2.4 million (Australian), it cannot afford the third. And some of that grant has gone to hiring extra nurses, merely to guarantee that patients randomized to early goal-directed therapy will have consistent health care worker attention throughout the 6 hours demanded by the Rivers protocol. Actually implementing the Rivers protocol, Dr. Peake admitted, is likely to be beyond the Australian system’s budget: “There really isn’t the existing infrastructure or resources to roll it out.”

Once data gathering is complete, in 2010, the ProCESS trial will deploy a separate cost-benefit analysis. As the trial rolls out—by the end of the summer, sites in Alabama, Arizona, Connecticut, Indiana, Massachusetts and Utah were recruiting — investigators said they were distressed by the media-driven focus on the large trial trumping the original one.

“The goal here isn’t to tear anyone down; it’s to put to rest anybody’s concern of, ‘Should I be doing this across the US, and across the world, based on 250 people in Detroit,’” Dr. Yealy said. “Wanting to follow up on someone’s work is the highest compliment.”

Conflict of interest statement: Truman J. Milling Jr., MD, the editor of this section, provided data to Dr. Rivers at his request for a research group performing a multicenter before and after trial of early goal-directed therapy in sepsis.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article, that might create any potential conflict of interest. The author has stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.


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The Patient-Centered Medical Home: A Solution to “Hamster Health Care” or a Drain on Emergency Care?

by ERIC BERGER
Special Contributor to Annals News & Perspective

A growing movement among primary caregivers to adopt a more patient-centric system of care has gained significant momentum during the last half decade, and if a raft of pilot projects show promising results it may lead to substantial changes in the allocation of health care resources, including those that now flow to emergency departments (EDs).

The movement, which has roots both among family physician-scholars as well as large employers such as IBM and The Dow Chemical Company, has coalesced into the concept of a “patient-centered medical home.” In a patient-centered medical home, patients have an ongoing, more direct relationship with a physician who provides comprehensive and culturally appropriate care, such as enhanced access, including same-day scheduling and expanded hours.

The growing enthusiasm for this model of care prompted the American College of Emergency Physicians (ACEP) to issue a position statement in August 2008, which urges caution in the implementation of a system that could negatively affect EDs.

Patient-centered medical homes have evolved during the last decade amid rising dissatisfaction among primary care physicians. Former British Medical Journal editor Richard Smith, MD, and health care futurist Ian Morrison, PhD, characterized this angst in 2000 as “hamster health care,” writing in the British Medical Journal: “Across the globe doctors are miserable because they feel like hamsters on a treadmill. They must run faster just to stand still. . . . But systems that depend on everybody running faster are not sustainable. The answer must be to redesign health care. . . . The result of the wheel going faster is not only a reduction in the quality of care but also a reduction in professional satisfaction and an increase in burnout among doctors.”

MAKING A HOME

Two years later, a pair of family physicians from the University of California, San Francisco, Kevin Grumbach, MD, and Thomas Bodenheimer, MD, were among the first to call for a “primary care home for Americans” in a 2002 Journal of the American Medical Association article.

Around the same time the American Academy of Pediatrics expanded its “medical home” concept from a simple repository of a patient’s records to include accessible, continuous, comprehensive, family-centered, coordinated, compassionate and culturally effective care.

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