

The following is an expanded letter that was sent as a reply to an article published in the *The Wall Street Journal* (WSJ) on August 14th titled **“New Therapy for Sepsis Infections Raises Hope but Many Questions.”** The original letter has not been published.

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Dear Mr. Thomson:

In April 2008, a reporter for a story that ran 3 months in your newspaper on August 14th interviewed Dr. Rivers. It was titled **“New Therapy for Sepsis Infections Raises Hope but Many Questions.”**

This reporter was provided background information, relevant publications and research prior to this article publication. Despite this, a non-peer reviewed article was produced that contained factual errors and critical omissions about early goal directed therapy (EGDT), its investigators and Henry Ford Hospital. The statements from this newspaper are in bold and the corrections follow:

.... "The new therapy typically costs about \$1,100 more per patient, by the estimate of Derek Angus, chief of critical care at the University of Pittsburgh."

Not true. There are three publications that show EGDT is cost effective which includes Dr. Angus and his colleagues.^{1, 2, 3}

.... "One concern I have is that this hypothesis has been accepted almost without debate by so many people," says Mitchell Fink, a professor of critical-care medicine at the University of Pittsburgh Medical Center."

EGDT has been recommended by founders of critical care and emergency medicine as far back as 1976.^{4, 5 6-11} EGDT was also derived from best practice recommendations or expert opinion at the time the study was constructed.⁴ These experts comprise the American College of Critical Care Medicine, which includes Drs. Fink and Angus.

...."For monitoring, he used a catheter, inserted in the jugular vein and slid to near the heart. If it showed that blood oxygen was too low, he elevated it with transfusions and often added a drug to make the heart beat harder. Dr. Rivers modified the catheter, which was made by Edwards Lifesciences Corp., and obtained patents for its design and use."

Not true. EGDT is not simply giving blood transfusions. It is, in fact, a recommendation for a sequence of changes in the approach to the critically ill patient. EGDT includes multiple important steps:

1. Early recognition of patients with a high risk of death.
2. Early cultures, source control and antibiotics
3. Fluid therapy titrated by central venous pressure.
4. Vasopressors if required to maintain blood pressure.
5. Maintaining hemoglobin concentration above 10 mg/dl using transfusions if required.
6. Maintaining central venous blood oxygen saturation above 70% using medication to make the heart beat stronger (increase inotropy).
7. Early use of positive pressure ventilation to decrease the body's need for oxygen with sedation if required.
8. Central venous oxygen saturation can be checked by intermittently drawing blood or continuously using the monitor.
9. You do not need the technology. The control group (or intermittent sampling) benefited with a decrease in their mortality as well (5-7%).¹² The goal is to apply EGDT as soon as possible without waiting hours to do it in the ICU.

....“That hospital (Henry Ford Hospital) held patents on a medical device critical to the therapy...”

Not true. The catheters used in the study were available and publically sold through Edwards Lifesciences before the EGDT study. Modifications were made on this product, which led to a patent on research years prior to the EGDT study.¹⁰ All of the catheters used prior, during and after the study published in 2001 in *New England Journal of Medicine (NEJM)* were purchased by Henry Ford Hospital from Edwards Lifesciences.

Since Edwards did not have rights to make a product based on the catheter modifications and patent claims until 2001, it is clear that the medical device was not used and critical to the therapy at the time of the study. The patent, owned by Henry Ford Hospital was never commercialized or generated revenue. Dr. Rivers declined all of his rights to the patent prior to the conduction of the EGDT study to avoid any conflict of interest.

.... ”Dr. Rivers and the hospital over the years have received at least \$404,000 from Edwards, the Irvine, Calif., company says.”

The EGDT study did not receive funding support from industry and was denied support from multiple academic funding sources. Dr. Rivers was compliant with all Henry Ford Hospital institutional policies regarding industrial relationships. These payments were received after the study was completed and over a period of 7 years (2001 to 2008). This includes a Henry Ford Hospital grant of \$150,000. This research support was used to support legitimate research-related costs for the institution and Emergency Department.

The patents mentioned above were never commercialized (brought no revenue), so Henry Ford Hospital released the rights back to Dr. Rivers and he in turn released the rights to Edwards Lifesciences after the study without direct compensation. Neither Dr. Rivers nor HFHS ever received royalty payments from the patents. Dr. Rivers declined over \$163,000-\$250,000 in potential royalty payments from Edwards Lifesciences to avoid any conflict or perceived conflict

of interest. Dr. Rivers has also declined any financial relationships with companies with related technology.

...."In a pivotal study he led, 133 sepsis patients got standard treatment and 130 his new therapy. In the New England Journal of Medicine in 2001, Dr. Rivers and colleagues reported death rates in the standard-treatment group of 46.5% but only 30.5% in those getting the new therapy"....."One problem critics now cite: Conventional therapy itself has generally produced death rates of 30% or lower, according to data from Australia and the Netherlands. Dr. Rivers's explanation is that his patients were sicker -- hence a higher death rate for those on conventional care".....Critics cite a statistical red flag: The study of the new therapy reported death rates for traditional care much higher than a number of other studies have found. Amid these concerns, the National Institutes of Health is beginning a large new study to re-evaluate the findings"..... He pointed to other studies he said corroborate his own. One, from China, does show a significant reduction in deaths with early goal-directed therapy, although it also has a high death rate with standard treatment that doesn't jibe with a number of other studies."

Not true. The ultimate confirmation of a study lies in reproducibility, generalizability and external validity. As provided to the reporter, over 7,000 patients in over 53 peer reviewed publications and abstracts have been studied since the EGDT study with a similar or better mortality benefit, see table below.¹³ This includes all ages, from children to the elderly with severe sepsis and septic shock.

More recently, a survey of over 4,000 patients comprising 40 centers and a meta-analysis shows similar or better mortality reductions using EGDT.^{14, 15} A repeat study of 714 patients (there were 263 patients in the original study) at Henry Ford Hospital by different researchers has shown similar outcome benefit.¹⁶ There are additional unpublished studies at present numbering thousands of patients, which will continue to support the original findings and basic principles of EGDT.

The patients at Henry Ford Hospital or those in the EGDT study were not sicker than patients in other studies. In a summary of current studies (from all over the world and the US), examining thousands of patients of many nationalities shows differently. These patients have similar illness severity (APACHE II scores) at baseline, sex, age, death rates and mortality reduction compared to the original EGDT trial. There has yet to be a single study in almost 7 years that has not demonstrated benefit with EGDT implementation.¹⁷⁻³³

Summary of Early Sepsis Intervention Studies

	APACHE II	% Male	Age	Patients Before N	Patients After N	Mortality Before-%	Mortality After-%	Mortality Reduction-%
15 Publications								
Mean	27.2	53.8	66.2	1072	1147	46.2	25.5	20.7
28 Abstracts								
Mean	23.0	58.9	61.4	2923	2771	43.8	24.5	19.3
43 abstracts and Publications								
Mean	26.1	55.1	64.5	4125	3328	44.6	24.97	19.6
EGDT Study								
Mean	21.4	50.4	64.4	130	133	46.5	30.5	16.0

.... *“The medical resident, who complained, Michael Donnino.”*

Michael Donnino was never involved or participated in the original EGDT study.

.....(1). *“Hospital statisticians who worked on it had concerns about the data and recalculated the results with all 288 patients, according to people familiar with the events. When they did, these people say, the death-rate gap wasn't statistically significant”*.....(2). *“Statisticians were especially concerned when they noticed that a relatively high proportion of the other 25 -- those not included in the final analysis -- were either conventional-therapy patients who survived or patients on aggressive therapy who died, say the people familiar with the events”*.....(3). *“But once patients are randomly placed in a group, they must be included in a final analysis, according to a fundamental principle of medical research. Twenty-five were not, the medical-journal article makes clear.”*

(1) Not true. All of the co-authors of the 2001 NEJM paper agreed with the analysis and the conclusions of the paper at its submission. This included two senior biostatisticians of which one was the Chairman of the Department of Biostatistics.

(2) Not true. The biostatisticians participating in an informal inquiry in 2005 concerning the original study reiterated their support of the analysis of the data. A third biostatistician, not involved in the original study, was asked by the Committee to re-analyze data using the original 263 patients plus the excluded patients of concern (in a hypothetical randomization of all patients). These data were analyzed for hospital mortality and 28- and 60-day mortality. Using a chi-square analysis weighted for the differences in illness severity (i.e., APACHE and SAPS scores) between control and treatment groups. This analysis demonstrated a statistically significant retained mortality benefit at all time points for the EGDT treatment group equal to or better than the original reported results of 263 patients.

(3) Not true. The hospital’s Internal Inquiry Committee consulted with external experts in clinical outcomes research and felt comfortable that the analysis and study design was appropriate. In other words, the patients of concern, when evaluated, did not affect the results of the study. This standard academic process and results was overseen and approved by the

Director of Research, Vice President of Academic Affairs, Chairman of Emergency Medicine and Chief Medical Officer of Henry Ford Hospital. A letter of full support also came from the CEO of the Henry Ford Hospital.

....”A large NIH-funded study to re-evaluate Dr. Rivers's early goal-directed therapy is under way at the University of Pittsburgh Medical Center. In contrast to the one-hospital study that launched the therapy, this one will include up to two dozen hospitals.”

Dr. Rivers and his colleagues conducted a study, which was also a quality initiative to prevent death from this disease at Henry Ford Hospital. This study was performed under very economical conditions after being denied extra-mural academic and industry funding on multiple attempts. They are humbled by the fact that this study has been adopted and continue to save thousands of lives not only at Henry Ford Hospital but also around the world. There is evidence that over 300 hospitals in the U.S. practice some form of EGDT as a standard of care indicating that they consider it best practice rather than research.

Summary

The story of EGDT was one of overcoming major obstacles and dedication by caring individuals at all levels of patient care. The opportunity to educate the public and save lives through a major communication venue was lost in an attempt to bring controversy. EGDT raises hope for a deadly disease. However, the questions raised and now remain relate to the reasons why this non-peer reviewed article suddenly appears 7 years after the EGDT publication.

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