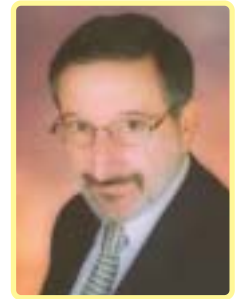


DOES USE OF A GUIDELINE REDUCE MORTALITY FOR PATIENTS WITH SEVERE SEPSIS? *by Herbert Patrick MD*



For this issue of Focus, we will discuss a Respiratory Care research project funded by an outside agency. An outside agency includes pharmaceutical companies, equipment manufacturers and private or government grant sources. We will continue to discuss each research project using the traditional Scientific Method format: Background or Introduction, Question, Hypothesis, Methods, Results, Conclusions, Reflections, Future Research, Bibliography, Acknowledgements, and Conflicts of Interest.

Edwards Lifesciences LLC, an international manufacturer of medical devices, sponsored this research project on patients with severe sepsis. Patients with severe sepsis are defined as having an infection causing a dysfunction in at least one organ system. For example, respiratory system dys-

function is defined as: (a) the presence of mechanical ventilation, or (b) $\text{paO}_2/\text{FiO}_2$ ratio below 250, or, (c) a respiratory rate above or equal to 20 breaths per minute or paCO_2 below or equal to 32 torr. In the past, patients with severe sepsis had mortality approximately 50%.

Edwards wanted to validate the findings of a new study of patients with severe sepsis at Henry Ford Hospital by Dr. Emanuel P. Rivers. His team used a guideline to treat patients with severe sepsis and significantly reduced mortality from 47% to 31%. Their research became a landmark article after being published in the *New England Journal of Medicine*.

However, some members in the medical community were concerned that the reduced mortality at Henry Ford Hospital might not be applicable to other hospitals. Therefore, Edwards chose to fund this project at four hospitals with an educational grant to each combined with an offer to use their Edwards PreSep[®] catheter for continuous measurement of $\text{ScvO}_2\%$. Measurement of $\text{ScvO}_2\%$, the saturation of central venous blood at the tip of this central venous catheter, was part of the 6-hour resuscitation bundle used in the guideline by Dr. Rivers. The guideline includes obtaining $\text{ScvO}_2\%$ values greater than 70% by 6-hours after onset of severe sepsis.

The design for this research project at our facility was retrospective, observational, and with a historic control. At first, we wanted to conduct a randomized, double-blind study. However, our IRB had advised that a randomized double-blind design for this study was not possible after the *New England Journal of Medicine* 2001 published guideline had become a clinical "standard of care". A standard of care cannot be withheld from patients as would be necessary with a randomized double-blind study.

Let's examine each of these terms for the research project design. Retrospective means looking back from the time of the newest (last) patient to be included in the study enrollment. Randomized means that each patient in the research project would be selected from the population of patients at our institution with severe sepsis without regard to any feature, such as attending physician, site of infection or prior medications. If randomization is successfully applied in a research project, then a single patient characteristic should not become a dominant component during the analyses of the data. Double blind means usage of the guideline for each patient would not be known by the researcher or by the patient. Historic control means that the control group would be comprised of patients treated prior to the institution of the guideline.

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Respiratory Research... *Continued from page 16*

As we have noted for other research projects funded by an outside agency, the first step between the principal investigator of the research project and the sponsor is the Confidentiality Agreement, also known as a Nondisclosure Agreement. The Confidentiality Agreement assures the sponsor that the principal investigator and other members of the investigative team will not disclose any research project related information into the public domain unless first approved by the sponsor. The public domain includes speaking to colleagues, publication of journal articles and book chapters, and presenting posters or slides at local, national, or international conferences. Edwards provided their standard Confidentiality Agreement for this research project.

The second step for research projects funded by an outside agency is submission of papers to the Institutional Review Board (IRB) describing details of the proposed research project. These papers describe the project design and include a consent form, if needed, for each subject to sign before enrolling and participating in the research project. IRB approval is necessary before initiating even the most superficial data gathering and certainly prior to enrolling subjects in the project.

The third step for research projects funded by an outside agency is creating a funding account for handling the finances of the project, including salaries and supplies. The funding is derived from a contract for receiving the unrestricted educational grant. A budget is needed for the total project, either tallied by subjects or by the calendar year. This budget is reviewed and approved by the outside agency and the financial officer at the site of the research project. Now let's review the research project:

The Background or Introduction of the research project explains interest in the topic and why the topic is significant. For this project, there is a high mortality of patients with severe sepsis. Validating a guideline for reducing mortality of patients with severe sepsis would save lives across the country, and correspond to the Institute for Healthcare Improvement (IHI) Saving 100,000 Lives Campaign. The use of the guideline should make for easier treatment of patients with severe sepsis and hence improve medical team compliance with the therapies. The guideline for patients with severe sepsis has four major milestones with an outcome greater than the sum of the effects of the individual treatments. This additive characteristic is called synergy.

The Question proposed is: Does the use of a guideline reduce mortality of patients with severe sepsis? (Note: The Question asked in every research project always has the possible answers: "yes" and "no.") The preconceived answer by researchers to the Question is called the Hypothesis. For this project, the Hypothesis was: Yes, the use of a guideline will reduce mortality of patients with severe sepsis.

For the Methods, the IRB decided that no Informed Consent was necessary as the project was observational only with data gathering. The goal enrollment was sixty patients treated using the guideline versus 20 patients as the historic control. Respiratory Care staff was involved in the data gathering for the project. Prior to physician insertion of the central venous catheter (CVC, PreSep®) into the patient's central vein, at either an internal jugular or subclavian

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approach, an in-vitro calibration of the ScvO₂ was performed. The ScvO₂ was continuously displayed on a bedside device, called the Vigilance' monitor. The guideline for patients with severe sepsis had four milestones in the first 6-hours: 1) obtain cultures and initiate antibiotics, 2) measure central venous pressure (CVP) from the CVC and administer fluids until the CVP was between 8 and 12 mmHg, 3) measure blood pressure (BP) and administer pressors until mean BP exceeded 65 mmHg, and, 4) measure ScvO₂ with the PreSep' CVC and Vigilance' monitor and administer packed cells followed by inotrope medications to maintain ScvO₂ above 70%. The data sheet for each patient and control had blanks for the time that each of the four milestones was obtained. These times were measured from the onset of severe sepsis. The duration of the project was adjustable so that 50 patients with severe sepsis treated with the guideline could be studied. Significant (t-test, $p < 0.05$) improvement in mortality at 28 days from onset of severe sepsis would indicate that the guideline for patients with severe sepsis was successful compared to the treatment of the historic controls.

To formulate the Results, patient data were analyzed using Tables and Figures. The table listed patient demographic characteristics for the 20 controls plus 50 patients. There was no statistically significant difference between these characteristics. The Figures were used to demonstrate physician compliance with the guideline using a flow diagram with the number of patients compliant at 6 hours for each of the four milestones. The last Table was the 28-day mortality in the historic control group of 20 patients versus the guideline treated group of 60 patients. Mortality of patients in the historic control group, $9/20 = 45\%$ was statistically different at $p < 0.05$ compared to the mortality of patients in the guideline treated group, $16/50 = 32\%$.

The Conclusion was that a guideline for treatment of patients with severe sepsis significantly reduced mortality. Therefore, in this project, the Hypothesis was supported, corresponding to a "yes" answer to the Question. (Note: When writing the Conclusion, the Hypothesis must be addressed whether it was supported or not.)

The Reflections offers an opportunity to critique the research project, suggesting possible modifications that would improve the quality of the research. For example, the patients with severe sepsis in the historic control group may not have received aggressive care as outlined in the guideline for patients with severe sepsis. Therefore, a statistically significant difference in the mortality of patients may have been easier to obtain with this study design. Reflections can also include a comparison with similar research projects.

Future Research is important because research should lead to more research. For example, this research project could lead to a larger, multi-site project based on the same experimental design.

References from similar research and the reference for non-parametric statistics are included in the Bibliography section.

Acknowledgement offers credit to those who assisted in the research project, both by time/effort and by financial support. The acknowledgement included Respiratory Care practitioners and nurses who participated and the unrestricted educational grant from Edwards.

Conflicts of Interest are listed for all Respiratory Care Practitioners and others participating in authorship of the project. Conflicts include ownership of stock or receipt of services or gifts from companies related to the project.



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