Commentary

Recently published papers: More about EGDT, experimental therapies and some inconvenient truths

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Abstract

This issue's recently published papers concentrates on early goal directed therapy, starting with new data from the original study through to new studies that may have a major bearing on the treatment of septic shock in years to come. A timely reminder about talking, walking and teaching clinical medicine completes the roundup.

Early goals

No one is likely to argue with the belief that prompt and appropriate treatment is effective and should be the standard of care. Back in 2001, Emmanuel Rivers and colleagues published their landmark study of Early Goal Directed Therapy (EGDT) [1]. Perhaps the central concept behind EGDT is that of oxygen debt and the secondary inflammatory insult inflicted by tissue hypoxia, which is modifiable with timely and aggressive cardiovascular support. A series of recently published papers emphasise and further elucidate this idea.

Firstly, Rivers and colleagues have published the results of a study of serum biomarkers of systemic inflammation from the majority of patients from their original study [2]. Patients had multiple biomarkers measured periodically over the first 72 hours of their illness. Two separate comparative analyses were performed. First, the protocol group are considered against the standard care group. Second, the whole patient population has been stratified into three groups by severity of admission global dysoxia (serum lactate and central venous oxygen saturations) and compared. Unfortunately, no third analysis of these three groups separated into those in the protocol and standard care groups was performed. Although this post hoc separation would have yielded statistically small groups, the results may well have provided useful hypothesis generation rather than statistically significant results. The results of the treatment comparison analysis demonstrate a statistically significant reduction in the level of all markers in the protocol group. However, the time course and magnitude of this difference is markedly different between the substrates. EGDT appears to obtund the early peak in interleukin 1 receptor antagonist and tumour necrosis factor alpha (although the baseline level was significantly higher in the protocol group). Perhaps the most striking difference however was in caspase-3, a marker of cellular apoptosis, the level of which fell dramatically in the protocol group and remained at a much lower level throughout the 72 hours, suggesting that EGDT reduced the secondary insult of oxygen debt. In the second analysis, unsurprisingly, the most dysoxic group at baseline had the highest and most persistently elevated levels of all the markers. Also noteworthy is the late (after 24 hours) but dramatic rise in caspase-3 in the middle group. Overall, this study provides additional and valuable biological plausibility to the oxygen debt hypothesis. I hope the third analysis suggested above is forthcoming.

Since the original EGDT trial, and following the advent of the Surviving Sepsis Campaign, there have been a number of published studies demonstrating the benefits of early protocolised care in patients with severe sepsis and septic shock. However, none have prospectively tested the EGDT protocol in a real world setting. Jones and colleagues have now done so [3]. Using a before and after design, they collected data for one year, on patients with septic shock attending their emergency department, then instituted EGDT and collected data for a further year. They observed 79 patients in the data capture group and 77 in the EGDT group. Their patient population differed significantly from the original study, being not as sick at presentation, but despite this, they found a mortality reduction from 27% to 18%. Protocolising care resulted in earlier administration of antibiotics, nearly twice as much crystalloid administration, a four times increase in the intubation rate and a doubling of vasopressor use in the first six hours. Of note, 40% of the

EGDT = early goal directed therapy; ICU = intensive care unit; SOFA = sequential organ failure assessment.

EGDT group also received corticosteroids as compared to just 6% of the non EGDT group. Though no doubt, the criticism will be levelled at this study that the observed group received suboptimal care, what this, and all of the other studies in this area have demonstrated, is that raising the profile of sepsis and implementing a time critical approach to care improves outcomes. Arguments about the elements of the protocol will no doubt continue as well, however, those with strong pro or con views would be best served by expending their time and energy designing and conducting clinical trials to provide an evidence base upon which to base future guidelines.

Inopressors

With regard to one such debate, the choice of vasopressor in septic shock, Annane and colleagues have published a prospective, multicentre, double blind, randomised control trial of epinephrine versus norepinephrine with dobutamine [4]. This study found no difference between the groups in mortality at 7, 14, 28 and 90 days, or indeed, serial sequential organ failure assessment (SOFA) score or a variety of haemodynamic end points. The study was prompted by limited evidence, and a physiological rationale, that norepinephrine, with dobutamine in the presence of a low cardiac index, is superior to epinephrine. The result of equivalence is perhaps less surprising than the authors suggest. Firstly, they recruited and randomised patients, on average, two days after intensive care unit (ICU) admission, during which crucial time period, a wide variety of supportive therapies had been used. Secondly, the investigators were only able to recruit one third of eligible patients, as always, raising the issue of the representative nature of the study sample. Thirdly, the power calculation for the study was based upon a mortality rate that far exceeded that observed in the study, thereby creating a significant chance of a type II error. Added to this, 95% of the study sample were intubated and ventilated with no agreed protocol on ventilation strategy, sedation or weaning, or indeed any other aspect of care with 19 units participating. Additional concerns include an average lactate of 4 mmol/l at study entry (after two days of ICU care), no information regarding cardiac index except the somewhat arbitrary target of >2.5 l/min/m^2 and the decision to target a mean arterial pressure of ≥ 70 mmHg. Given all of these concerns, the only hypothesis this study supports is that both inopressor strategies are equally effective at achieving the haemodynamic goals set.

To add further evidence to the EGDT strategy, Sennoun and colleagues have published a study comparing different resuscitation strategies in a rat endotoxic shock model [5]. They compared no treatment to fluid only, norepinephrine only, fluid and delayed norepinephrine and fluid with immediate norepinephrine. Perhaps unsurprisingly, the fluid plus immediate norepinephrine group faired best, followed by the fluid plus delayed norepinephrine. Both fluid alone and norepinephrine alone significantly ameliorated the endotoxic shock but to far less a degree than combined therapy. The model falls short of the complexities and heterogeneity of the clinical arena but supports two important ideas. Firstly, that prompt resuscitation to maintain flow and pressure are important. Secondly, conventional teaching that volume resuscitation should precede vasopressor support may, in fact, be bad dogma.

Mitochondrial therapy

Continuing with the oxygen debt theme, much attention has fallen on the relative contributions of microcirculatory and mitochondrial failure in sepsis. With regard to the latter, Piel and colleagues have published the first trial of a successful mitochondrial therapy in a mouse caecal ligation and puncture model [6]. Using a complex experimental design, the authors successfully replenished cytochrome c levels and activity in the mitochondria of mouse myocardium by exogenous administration of bovine ferrocytochrome c. The most compelling data comes from the left ventricular monitoring which demonstrated a $>45\%$ increase in left ventricular work 30 minutes after injection of ferrocytochrome c in animals subjected to caecal ligation and puncture 24 hours previously. How long before this and related work reaches clinical trials in humans is unknown but might mitochondrial therapies yet prove to be the therapies that end the optimal inopressor debate?

Hydrogen?

Staying in the realm of novel therapies, hydrogen may also be in ICUs in the future. My personal interest in hydrogen as a therapeutic gas was ignited (pardon the pun) by a paper by Gharib and colleagues [7], who five weeks after infecting mice with schistosomiasis subjected half to two weeks of breathing a hydrogen oxygen atmosphere and half to nitrogen oxygen. The anti-inflammatory effects of the hydrogen were very striking. The impracticality of repeating this study in any clinical setting, due to the explosive risk, relegated it to a fascinating but essentially irrelevant curiosity. However, it appears that hydrogen therapy can be safely administered and with impressive effects. A Japanese group have published two papers [8,9] demonstrating the therapeutic potential of hydrogen in ameliorating cellular injury caused by ischaemia and reperfusion. The rationale is that hydrogen is a potent scavenger of oxygen free radicals (considered major players in cellular damage) and, as the authors state, "unlike most known antioxidants, which are unable to successfully target organelles, it has favourable distribution characteristics: it can penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus."

In the first study [8], they performed a series of experiments starting with cell cultures and moving onto rats, whom they subjected to surgical occlusion of the middle cerebral artery for 90 minutes followed by reperfusion for 30 minutes. They administered four different gas mixtures to four groups of animals. All of the mixtures contained 30% oxygen. The

groups received 0, 1, 2 or 4% hydrogen with the balance made up by nitrous oxide. The animals exposed to 2 and 4% hydrogen had dramatically reduced infarct volumes compared to the others, though interestingly the 2% group appeared to fair best. Of note, hydrogen was only effective if administered during reperfusion. The authors helpfully state that hydrogen presents no risk of explosion at concentrations below 4.7%. To make it even more user-friendly they suggest an alternative method of administration by dissolving hydrogen in normal saline and giving it intravenously.

The same group, in a separate paper [9], report an experiment in which they subjected mice to an ischaemic reperfusion injury to the left lobe of the liver. They used the same four gas mixtures on four groups of animals. The results are equally dramatic with a marked reduction in cellular injury with increasing doses of hydrogen.

Clinical teaching

Finally, I would like to promote the Viewpoint of Brendan Reilly [10]. This gentleman, who has been teaching clinical medicine for more than 30 years, has been inspired by the recent and widely discussed Al Gore global warming documentary. The inconvenient truths that Dr Reilly wishes to publicise surround the demise of clinical teaching. He offers some excellent advice, not only on how to talk the TALK but also walk the WALK, and for once I applaud the inventive use of stolen acronyms.

Competing interests

The author declares that they have no competing interests.

References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock.** *N Engl J Med* 2001, **345:**1368-1377.
2. Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R, Childs EW: **The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock.** *Crit Care Med* 2007, **35:**2016-2024.
3. Jones AE, Focht A, Horton JM, Kline JA: **Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock.** *Chest* 2007, **132:**425-432.
4. Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, Troche G, Ricard JD, Nitenberg G, Papazian L, *et al.*: **Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial.** *Lancet* 2007, **370:**676-684.
5. Sennoun N, Montemont C, Gibot S, Lacolley P, Levy B: **Comparative effects of early versus delayed use of norepinephrine in resuscitated endotoxic shock.** *Crit Care Med* 2007, **35:**1736-1740.
6. Piel DA, Gruber PJ, Weinheimer CJ, Courtois MR, Robertson CM, Coopersmith CM, Deutschman CS, Levy RJ: **Mitochondrial resuscitation with exogenous cytochrome c in the septic heart.** *Crit Care Med* 2007, **35:**2120-2127.
7. Gharib B, Hanna S, Abdallahi OM, Lepidi H, Gardette B, De Reggi M: **Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation.** *C R Acad Sci III* 2001, **324:**719-724.
8. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S: **Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals.** *Nat Med* 2007, **13:**688-694.
9. Fukuda KI, Asoh S, Ishikawa M, Yamamoto Y, Ohsawa I, Ohta S: **Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress.** *Biochem Biophys Res Commun* 2007, **361:**670-674.
10. Reilly BM: **Inconvenient truths about effective clinical teaching.** *Lancet* 2007, **370:**705-711.