Editorials

Therapeutic options for head injury in intensive care

Treatment strategies in traumatic brain injury have been based primarily on pathophysiological principles. Over 200 years ago, the Monroe-Kelly doctrine was described - small increases in intracranial volume result in marked increases in intracranial pressure.[1,2] The concept of exhausted intracranial elastant reserve is as valid today as it was in the past, particularly when reviewing past, current and new therapies for traumatic brain injury.

Fifty years ago, pioneering work by Guillaume and Janny identified intracranial hypertension as the prime pathophysiological entity in traumatic head injury.[3] In 1960, Lundberg described continuous measurement and ventricular drainage in patients with head injury.[4] So began an era of pioneering work that focussed on treatments aimed at the reduction of intracranial pressure. Therapies such as osmotherapy, hyperventilation, steroids, hypothermia, barbiturate coma and decompressive craniectomy, for which sound physiological arguments exist to reduce intracranial pressure, were applied with varying degrees of enthusiasm to heterogeneous groups of head injured patients. However, the efficacy and effectiveness of almost all of these treatments have not been subjected to scientific evaluation. The evidence-based Brain Trauma Foundation guide-lines for management of severe head injury, highlight the paucity of evidence that exists for these "time-honoured" therapies.[5]

Apart from the degree and mechanism of primary injury, the recognition that the magnitude of secondary brain injury (particularly systemic hypotension), is the most important, independent, determinant of outcome,[6] has led to a "resuscitation" based approach to head injury management, where maintenance and augmentation of cerebral perfusion pressure has taken precedence. Increasingly, this approach is being questioned, as pathological changes over time following injury are recognised.[7,8]

In recent times, the focus of researchers in traumatic brain injury has been directed at modulation and manipulation of agents responsible for post-traumatic intracranial inflammation. A large number of phase I and phase II studies in animal models of reproducible head injury with definable primary outcomes, quantifying the cellular mechanisms of primary head injury, have been published. Unfortunately, the translation of positive results from these phase II studies into clinical trials has not been forthcoming.[9-11]

In this issue of Critical Care and Resuscitation, a review of the role of indomethacin in the management of traumatic brain injury is presented.[12] The authors provide a summary of the pathophysiological basis of a non-specific agent such as indomethacin and list the small number of inadequately powered studies with variable, often surrogate, outcomes. Not surprisingly, they conclude correctly that on the basis of current evidence, indomethacin should only be considered as an experimental therapy for refractory intracranial hypertension.

There are many confounding variables that make conducting a randomised controlled trial of a clinical intervention (let alone a single neuromodulating agent) directed at improving outcome from traumatic brain injury, logistically difficult. These variables include casemix variation between centres, assessment and standardisation of the initial injury, controlling for the degree of secondary insult and lead time bias before appropriate resuscitation, degree of extracranial injuries, standardisation of resuscitation, intensive care unit protocols, monitoring thresholds, operative interventions and quantification of outcomes. Given the caseload of even the largest neurotrauma centres, multicentred studies are required to adequately power such studies.[13]

In developed countries, the incidence and severity of traumatic brain injury is decreasing primarily due to public health initiatives such as seatbelt, helmets, drink-driving and speeding legislation, improved roads and motor vehicle technology. It would appear that these initiatives, combined with improved pre-hospital emergency care and integrated trauma systems, are more effective in improving outcomes rather than medical treatments applied in the intensive care unit some time after the primary injury.

The factors outlined above have resulted in a degree of therapeutic nihilism about medical treatments for traumatic brain injury. However, renewed interest in two "old" therapies (i.e. corticosteroids and decompressive craniotomy) are leading clinical interventional research.

Early steroids may modulate the development of intracranial inflammation and raised intracranial pressure. The results of a large randomised, placebo-controlled trial on the effects of a 48-hour infusion of corticosteroids on death and neurological disability in adults with head injury and impaired consciousness (CRASH trial: www.crash.lshtm.ac.uk) are awaited. The CRASH investigators are applying a strategy akin to thrombolysis trials in acute myocardial infarction, recruiting a very large patient cohort using a simple,

single intervention and measuring mortality. However, it is sobering to note that this study has a projected sample size of 20000 patients recruited from over 70 countries. At the time of publication of this editorial, only 4000 patients will have been enrolled since April 1999.

Increasing interest in the role of early, pre-emptive, decompressive craniectomy has led to the development and commencement of studies in Australia, United States of America and Europe. These studies are primarily based on the Monroe-Kelly doctrine, recognising that refractory intracranial hypertension in its own right as a potentially avoidable secondary insult. By increasing the "space" in the intracranial vault early, thereby improving intracranial elastance, pathological intracranial hypertension may be both reduced and minimised. The challenge in these trials is to identify the patient subset that is most likely to respond. With a potentially smaller pool of patients, it will be necessary to conduct a study on a targeted population. In both these studies, mortality may not necessarily be most important outcome, rather, improved functional outcomes of survivors.

Despite over 200 years of clinical experience and intense research initiatives, the all-cause mortality of traumatic brain injury remains distressingly high. The financial, social and emotional impact of disabled survivors on the community is substantial. The key to improving survival from traumatic brain injury will remain with public health, environmental and educational initiatives. In countries with high quality pre-hospital emergency systems and intensive care management, significant improvements in functional outcome from current levels are unlikely. However, the challenge is to maintain these standards and to develop strategies that have applicability to both developed and developing countries.

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Keeping continuous renal replacement therapy - continuous

Continuous renal replacement therapy (CRRT) has become widely utilised in the supportive treatment of critically ill patients with acute renal failure (ARF). The acclaimed benefit is the haemodynamic stability it achieves whilst controlling both azotaemia and fluid and electrolyte status.

Nevertheless, despite its widespread use, there is a paucity of controlled data demonstrating survival benefit with CRRT techniques. The data that are available are also conflicting.[1-4] While the goal of therapy, with variously prescribed dialysis and filtration

rates, was initially aimed at improving control of azotaemia and water balance, current data suggests that the volume of ultrafiltration and perhaps the magnitude of convective clearance may be equally important to achieve the improved survival rates.[1,2] Regardless of the CRRT prescription, its continuous and uninterrupted application is crucial to the haemodynamic stability and efficacy. However, keeping CRRT circuits going safely is a major challenge. In this edition, Fealy *et al*,[5] highlight the reality that CRRT is indeed not continuous and there is significant circuit "down-time".

The CRRT down-time is the result of circuit duration, the frequency of circuit change and the time taken to effect the change. Fealy *et al*, have shown that a long down-time predictably reduces plasma urea and creatinine clearance. They also highlight that any difference between the prescribed and delivered "CRRT dose" may inadvertently result in failure to achieve the ultrafiltration targets that have been associated with the survival benefit.[2] On a more practical level, long down-times can also contribute to haemodynamic instability due to vasodilatation when off CRRT and a reduction in preload when running on. Furthermore, if the long down-time is due to a short circuit duration and frequent circuit changes, significant blood component loss can result. There is also an increase in cost due to increasing consumables and demand on nursing time.

Circuit down-time due to the time taken to change the circuit is really a logistical problem and is dependent on staff availability, motivation and expertise. For this reason, CRRT down-time may a useful marker of quality of care. The challenge in reducing down-time is to prolong circuit duration safely. Currently, we recognise the "CRRT savvy nurse", the crucial role of the free flowing Vascath®, the benefit of pre-emptive flow reductions prior to suction and patient positioning and the importance of rapid problem solving. However, the science of prolonging the CRRT circuit life is less clear. We know that some patients benefit from anticoagulation, but there is little science in predicting which ones do and how much anticoagulation is needed. Achievement of adequate circuit life without anticoagulation is well documented. We also know that anticoagulation for CRRT adds to the risk of haemorrhage in the critically ill patient and this needs to be balanced against the benefit of CRRT and circuit duration.

There are several reasons why our approach to maintaining CRRT circuits remains largely empirical. Firstly, critically ill patients with ARF are complex and their coagulation status is variable. Several techniques for circuit anticoagulation have been tried. Unfractionated heparin is the most commonly employed anticoagulant and it effectively prolongs circuit life.[6] Surprisingly, the degree of heparinisation, as measured by the activated partial thromboplastin time, has been shown not to influence circuit life.[6,7] This would suggest that other components of the coagulation system, in addition to the intrinsic pathway, may be more important.

While the study by Fealy *et al*, found that platelet count effected circuit down-time, presumably by reducing circuit life, we did not observe this,[6] although we found in earlier work, that a rising platelet count during the life of a circuit did significantly reduce the circuit life.[7] It would seem that platelet numbers and function are important in determining circuit life and, in keeping with this, prostaglandin infusions, alone or in addition to heparin, appear to be of benefit.[8] In the hope that platelet function would be better assessed by using thromboelastography (i.e. a global measure of coagulation), we found that some thromboelastograph parameters correlated with circuit life.[6] However, we were unable to predict which patients would need heparin. Other anticoagulation techniques such as regional heparinisation and citrate infusions have not been shown to be more effective at prolonging circuit life and are not widely used.

There are several other problems with the study of anticoagulation and circuit life. Not all circuits are changed because of elective discontinuation or circuit clotting. Circuits lost because of inadequate anticoagulation demonstrate a steady rise in haemofilter resistance and pressure gradient over a period of time. Many circuits that are thought to have been lost because of clotting often do not demonstrate this gradual pressure gradient rise. These circuits have a transient interruption in flow and clot secondarily. The problem with these circuits is not the level of anticoagulation but the sudden reduction in flow. We found in two studies that the pressure criteria of clotting is only documented in 62% and 71% of circuits.[6,7] In as many as 15% of circuits, failure is due to a presumed transient flow interruption, often due to Vascath® problems or delayed trouble-shooting of transient flow problems. When examining the effect of coagulation status and circuit life it is important to include only circuits that meet the "clotted" criteria (e.g. a steady rise in haemofilter resistance and pressure gradient), which were not considered in the study by Fealy *et al*.[5]

The statistical analysis of the effect of coagulation parameter on circuit life also presents a problem. The coagulopathy of critically ill patients with ARF is quite variable in extent and nature and CRRT circuits behave differently between patients. Therefore, to allow an analysis of all circuits, data should be analysed using random effects regression (mixed models) with the patient fitted as a random factor. Mixed models take into account the interdependence of observations within patients, while allowing treatment effects to be estimated using both within-patient and between-patient information.[9]

We are in even less control of circuit life with the newer generation of CRRT machines. These machines have more flow shut down alarms, which differ between machines. The alarm thresholds are not obvious, largely unsubstantiated and are not routinely calibrated. Gone is the ability to push up flow shutdown thresholds for difficult cases, which we had with the "old blue boxes". Tolerance of high circuit pressures resulting in increased circuit longevity could be achieved with these Gambro® blood monitors without causing obvious adverse effects such as haemolysis.[10] Most machine manufacturers also market circuit consumables, and the obvious association between low threshold pressure shutdown alarms and frequent circuit changes demands greater substantiation of these thresholds.

The future for renal replacement therapy in critically ill patients lies in two directions. One is in keeping CRRT continuous and striving for safe continuous application with the help of new technologies such as anticoagulant bonded circuits. The other is to abandon the goal of continuous and move towards discontinuous renal replacement therapies of sustained low-efficiency daily dialysis (SLEDD) or extended daily dialysis (EDD) which have been shown to be effective techniques in the critically ill patient.[11,12] These hybrid techniques achieve the prescribed dialysis dose over periods of 8 - 12 hours and in one center is performed overnight to allow unrestricted access to patients during the day.[11] Bellomo *et al*, in this issue of Critical Care and Resuscitation introduce us to the benefits and pitfalls of these new techniques.[13]

In the meantime, while the science of these issues is being defined, we have to continue to work on the art of keeping CRRT continuous.

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Paediatric haemoglobin level: when should we worry?

Surveys of transfusion practice in critically ill patients[1] in themselves portend to a problem with regard to a lack of evidence based algorithms for our patients. In a specialty that prides itself on knowledge and expertise in improving oxygen delivery, it is hardly acceptable to use authoritative recommendations based on observational studies.[2] Absolute haemoglobin levels are at the core of oxygen delivery and utilisation.

In modern intensive care practice, the clinical dilemmas are when to transfuse and what haemoglobin (Hb) level is ideal.

When to transfuse the critically ill paediatric patient is not a simple decision. It is determined by personal preference, underlying causes and chronicity of anaemia and likelihood of other factors influencing oxygen

delivery (e.g. shock, hypoxia). However, the initial clinical consideration should be directed toward transfusion minimisation strategies, such as controlling ongoing blood loss, maximising oxygen delivery by improving cardiac output and supplemental oxygen, minimising oxygen consumption (e.g. sedation, temperature control) and, in the longer term, stimulation of haematopoiesis (e.g. iron, folate, vitamin B_{12} and erythropoietin).

Complications of transfusion in paediatrics can be severe. Massive transfusion, in particular, may lead to fluid overload, hypothermia, coagulopathy, hyperkalaemia followed by hypokalaemia, acute respiratory distress syndrome and citrate toxicity. In paediatrics, massive transfusion means replacement of one blood volume (e.g. 75 mL/kg for children under 1 year of age and 70 mL/kg for over 1 year of age) and is most likely to occur during resuscitation in major trauma, orthopaedic surgery, surgery for malignant disease, cardiopulmonary bypass surgery and extracorporeal membrane oxygenation.

More chronically serious problems are transmission of infectious diseases (e.g. hepatitis B and C, HIV and CMV), alloimunisation (antibodies against leukocyte HLA antigens) and graft vs. host disease caused by proliferation of donor viable T lymphocytes. Graft vs. host disease is prevented by irradiating donor blood, which should be given to all neonates, patients receiving bone marrow or stem cell transplantation, patients at risk of immunocompromise and directed relative donation. Because some inherited immunodeficiency diseases have late onset manifestations (e.g. Di George syndrome, severe combined immunodeficiency), it is worth considering irradiating all blood given to patients under one year of age.

In the end, the clinical decision on when to transfuse is usually determined by the extent of the anaemia, the underlying disease and risk minimisation, with the process of risk minimisation pushing of the boundaries for lower haemoglobin levels. But what is that lower limit? Do patients with cyanotic congenital heart disease whose oxygen delivery is severely compromised need haemoglobin levels of 120 g/L? Can uncomplicated major postoperative orthopaedic cases accept haemoglobin levels as little as 60 g/L? Where is the evidence for these practices? In the end decisions are often made for individual patients based on assessment of symptomatology and clinical signs of decompensation.

Paediatricians delight in formulae, which rightly allow for consistent management of patients across age groups. Formulae can determine the volume required to reach an ideal haemoglobin, for example: a) [Hb (ideal) - Hb (actual)]/Hb (ideal) x 70mL/kg and, b) 3 mL/kg packed red cells increase haemoglobin by 10 g/L. Nevertheless, when a decision to transfuse has been made, for a paediatric patient, a strategy that minimises risk seems the most appealing. This means ignoring paediatric formulae and not aiming for an "ideal" haemoglobin, but giving the maximum volume that can be clinically accepted by the patient (e.g. 10 - 20 mL/kg) at a rate determined by need. This rate will be rapid in the presence of hypovolaemia, but otherwise more slowly and given over the maximum period allowable for blood to remain unrefridgerated above 4^{o}C (usually 4 hours).

In the end, surveys of any clinical practice are important in that they highlight deficiencies in clinical decision making and hopefully result in further evaluation, more rigorous assessment and evidence based practice.

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Learning new lessons or repeating old mistakes?

The recent publication in the New England Journal of Medicine of a number of articles,[1-4] looking again at the question of the efficacy of recombinant activated protein C or APC (Xigris®, Eli Lilly) in severe sepsis as originally reported in the PROWESS trial[5] and the response of the primary investigators of the latter trial,[6] has some resonance with the "second look" saga[7-10] that surrounded the publication of the original HA-1A monoclonal antibody study[11] and the corresponding response of the HA-1A trialists.[12] This debate is even more ironic when one considers that some of the "critics" of both trials are the same and the recommendation for licensing of the now withdrawn HA-1A apparently occurred with unanimous approval by the United States Food and Drug Administration (FDA) advisory panel;[12] whereas the FDA Anti-Infectious Drugs Advisory Committee is reported to have been split 10 to 10 as to the safety and efficacy of APC.[3] The purpose of two of the papers above[2,3] was to alert

readers to some of the potentially contradictory trial detail amassed in the licensing process of APC and the effect that this could have on the overall interpretation of the original report;[5] in particular, study protocol amendments, change in APC master cell line, sub-group efficacy and adverse events (e.g. bleeding). For the clinician, the practical interpretation of a single reported trial[13] has become both onerous and uncertain; particularly as publicly available electronic material, in this case, FDA reports and submissions,[14-18] is not routinely accessible and runs into hundreds of pages.

With respect to the PROWESS trial, the response of some recent editorialists[19,20] has been, perhaps not surprisingly, cautious; provoking one commentator to lament the lack of excitement about the trial.[21] The contrasting results of the PROWESS (positive treatment effect) and the antithrombin III (ATIII) KyberSept (null effect) sepsis trials have been reviewed,[22] as have the putative pathophysiological mechanisms,[23] in particular the role of heparin, both as an anti-sepsis agent[24] and in terms of adverse effects.[22] Of note was the difference in mortality rate of the placebo group in each trial: KyberSept 38.7% and PROWESS 31.3%, p = 0.001 (Fisher exact test), suggesting difference in illness severity on enrollment (unfortunately the PROWESS study used APACHE II and the KyberSept study used SAPS II as severity instruments). Both studies exemplified the limiting requirements of controlled clinical trials methodology, particularly those of patient selection, and such limitations have been the subject of formal review.[25]

Patient selection is particularly pertinent in consideration of the treatment effect of the now licensed APC product. Although the exclusion criteria were provided in Appendix 2 of the original report,[5] what was not mentioned was the substantial protocol amendment at 720 (of 1690) enrolled patients plus a change in APC master cell production line. The sponsor detailed these amendment changes (10 points) in the FDA submission[18] and the trialists explained them in terms of enrolling ".. patients with a high likelihood of dying from severe sepsis and a low likelihood of dying from other causes...." and excluding "...patients in whom life support might be curtailed during the 28-day study period..." (see also Table 1 in their response).[6] Surprisingly, there was no change in placebo group mortality subsequent to the amendment (30% before and 31% afterwards), but there was a change in the efficacy of APC from null to active (relative risk (RR) 0.94, 95% CI 0.75 - 1.17, p = 0.57 to RR 0.71, 95% CI 0.57 - 0.87, p = 0.001; interaction test, p = 0.08) and such drew detailed comment from Warren *et al*, Siegel and the FDA.[2,3] No convincing evidence was adduced for a role of either protocol amendment or the concomitant new master cell bank in this efficacy change, but such cannot be excluded.

The sponsor noted that the "95% relative risk confidence intervals for the original and amendment results both include the overall relative risk estimate for the trial of 0.806, and ...there was considerable overlap in the relative risk confidence intervals of the two subpopulations".[18] However, the inferential strategy of using overlapping CI is biased to the extent that it rejects the null hypothesis less often (that is, it is a conservative measure).[26] The sponsor strategy for demonstrating consistency of effect across trial sub-groups, overlap of 95% CI of the various sub-group treatment effects (approximately 70) with the overall study relative risk estimate (0.806), produced different estimates of treatment consistency compared with that adopted by the FDA and by Warren *et al*, who argued for severity dependence of treatment. As shown in Table 1 in Warren *et al*,[3] the first two APACHE II quartiles had no significant treatment effects, using the more familiar definition of the null effect as 95% CI spanning 1.

A number of issues are raised here about the sponsor's analytic strategy, which, as Ely *et al*[6] mentioned, resulted in "only one .. not meet[ing] the trial definition of subgroup consistency." First, it is problematic using the point estimate of 0.806 as a null hypothesis in that this is based on the same data as the subgroups being tested; second, how likely is it with multiple testing that one should obtain fewer false positives than statistically expected (at p = 0.05); third, the correspondence between confidence intervals and hypothesis tests (that is, point estimate as null hypothesis) does not always hold, depending on the calculations of the standard errors; fourth, the method of overlap of CI is sensitive to the study design (it will be deficient in a randomised trial context when standard errors of the two populations are similar) and the correlation between point estimates (with a positive correlation, likely in a trial context, the overlap method loses power).[26]

Apropos of consistency of effect, it was of more than passing interest to note that in the sponsor submission,[18] the first APACHE II quartile group was effectively deemed discordant (unadjusted RR point estimate of 1.25 with lower 95% CI was 0.78) and a lengthy analysis was undertaken in an attempt to explain this, presumably on the basis that all other APACHE II quartile point estimates were < 1, which argued, in some sense, against consistent sub-group effects. Paradoxically, no such analysis was undertaken to explain a RR of < 0.5 with upper 95% CI < 0.806 (treatment benefit greater than the entire population) in the 1st IL-6 quartile group.

The sponsor further suggested that the "..observed variability in relative risk estimates...[of treatment effect]...appears predominantly due to changes in the mix of investigators actively enrolling patients during

the course of the trial..."; 20 sites enrolled patients only under the original protocol version, 45 investigative sites only under the amended version of the protocol (227 patients). The treatment-by-protocol interaction for the 99 sites enrolling under both protocols was non-significant at $p = 0.5$.[18] Evidence of a treatment-by-site interaction effect was present at $p = 0.08$ (over the 160 sites).[27] Of interest was the lack of treatment effect (95% CI of RR spanning 1) in the regional areas of both Europe and Australasia.[28] Such effects must, of course, be tempered by the known problems of post-hoc sub-group analysis.[29]

The original publication[5] and the sponsor submission to the FDA Anti-Infective Drugs Advisory Committee[18] argued for a consistent treatment effect of APC across subgroups, but the FDA licensed the product for treatment of adult patients with severe sepsis and an APACHE II score of 25 or more (3rd and 4th quartiles, see above), the latter requirement still being effectively an untested hypothesis. Using simulation studies in an economic evaluation, Manns *et al*,[1] gave further credence to an APACHE II treatment threshold in terms of cost effectiveness, but although the mean APACHE II score of their cohort (787 patients) was 21, only 40 patients were sampled for formal chart review to confirm a diagnosis of severe sepsis, suggesting the potential for insensitivity of sepsis diagnosis. At this stage the requirement for a second blinded efficacy trial has not been mandated for APC as opposed to the HA-1A case[30] where severe doubts about the activity of the monoclonal antibody were expressed.[31] Ely *et al*,[6] commenting upon the difficulties inherent in the use of an APACHE II treatment threshold, referred to the complementary evidence from organ dysfunction scores where treatment-induced RR showed a progressive fall from 0.92 through 0.6 with organ systems dysfunction of 1 to 5.[18] However, the 95% CI of the RRs all spanned 1, suggesting that organ dysfunction was an insensitive means of assessing risk-related treatment effects and therefore an unsatisfactory surrogate.

Given that one of the reasons proffered for the differential efficacy between APC (some) and ATIII (none) in sepsis was the superior anti-inflammatory of APC,[23] it was surprising then that the only significant and consistent organ system (time) change (either 28 day mean-time average or time-windowed, days 1 - 4, 1 - 7 and 1 - 14), treatment versus placebo, was in the cardiovascular system. Using Kaplan-Meier estimates with non-surviving patients censored, time to resolution of both cardiovascular and respiratory organ dysfunction was significantly reduced with APC ($p = 0.009$).[18] This was also reflected in a significant treatment decrease in vasopressor (20.1 versus 18.8, $p = 0.014$) and ventilator free days (14.3 versus 13.2, $p = 0.05$), although, paradoxically, not in SIRS-, ICU-, or hospital-free days.

However, the strategy of censoring deaths with Kaplan-Meier estimates depends upon the assumption of "non-informative censoring" and this has been questioned in acute illness.[32] The study methods for dealing with missing data were also problematic: for imputation, last observation available was carried forward (LOCF), an ad hoc method known to be based upon unrealistic assumptions;[33] for informative drop-outs (deaths), a non-surviving patient received an organ dysfunction score of 4 (worst score) for the day of death and for every day thereafter until Study Day 28. The latter scenario, where there is no joint modeling of the marker level and drop-out process, has been shown to yield biased estimates.[34]

With respect to the FDA assessment of the efficacy of APC,[14] the following groups were identified where treatment effect predominated: 3rd and 4th APACHE II quartiles, laboratory evidence of disseminated intravascular coagulation, not on heparin, age > 50 years, shock and $\geq$ 2 organ system dysfunctions.

Where then does this leave the clinician? Obviously treatment efficacy has retreated from a uniform effect,[5] the absolute magnitude of which may not be as great as initially reported,[35] to one located in sub-groups, albeit some pre-defined and intuitively obvious. The conclusion must be with Warren *et* al,[3] that APC should not be a standard of care in severe sepsis and, despite some evidence for cost effectiveness if tailored to an APACHE II threshold, a confirmatory trial is mandatory.

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