Critical Care 3

Critical care: advances and future perspectives

Jean-Louis Vincent, Mervyn Singer

Intensive care offers a standard of monitoring, intervention, and organ support that cannot be readily delivered in a general ward. Its expansion in the past few decades, including the creation of emergency and outreach teams, emphasises that intensive care has an increasingly prominent role within the hospital. Although outcomes are clearly improving, intensive care remains a nascent specialty in which we are still learning how to harness a powerful ability to manipulate physiology, biochemistry, and immunology to achieve best outcomes for the patient. The results of many multicentre studies have not lent support to, or have even confounded, expectations, drawing attention to several issues related to patient heterogeneity, trial design, and elucidation of underlying pathophysiological processes. However, these results have generated constructive introspection and reappraisal of treatments and management strategies that have benefited the patient. In addition to the medical, financial, and logistical challenges in the future, exciting opportunities will arise as new developments in diagnostic tests, therapeutic interventions, and technology are used to exploit an increasing awareness of how critical illness should be managed.

Published Online
October 9, 2010
DOI:10.1016/S0140-6736(10)60575-2

See Online/Comment
DOI:10.1016/S0140-6736(10)61502-4

This is the third in a Series of three papers about critical care

Department of Intensive Care, Erasme Hospital; Université Libre de Bruxelles, Brussels, Belgium (Prof J-L Vincent MD); **and Bloomsbury Institute of Intensive Care Medicine, Department of Medicine, University College London, London, UK** (Prof M Singer FRCP)

Correspondence to:
Prof Jean-Louis Vincent, Department of Intensive Care, Erasme University Hospital; Route de Lennik 808, 1070 Brussels, Belgium
jlvincen@ulb.ac.be

Introduction

The intensive care unit (ICU) nowadays bears little resemblance to the early versions set up after the poliomyelitis epidemics in the 1950s. Yet, apart from obvious differences in design, technology, and uniforms, what real advances have been made and what does the future hold? Here we summarise what we believe to be the most important features of progress in intensive care medicine in recent years, and suggest key challenges and opportunities for the future.

ICU and ICU patients

A characteristic of the ICU population is its substantial heterogeneity, which presents a challenge in clearly defining who or what an ICU patient is. Differences exist in the age and sex of patients; type, trajectory, and duration of the disease process; comorbidities; and manner and severity of complications. All of these aspects can affect outcomes, as can the source of patient admission. Patients admitted from general wards have overall worse outcomes than do those admitted from the emergency department or operating theatre;[1] patients transferred from other hospitals fare even worse than do those transferred from within the same hospital.[2] The existence of a complex interplay between disease severity and lead time means that if patients admitted with established, severe multiple organ failure were admitted earlier when the degree of severity was lower, their chances of survival would be improved. Moreover, the ICU is only one geographical location within the disease continuum; outcomes also depend on the types of management before and after the patient's stay in the ICU. Indeed, physicians or nurses working in the ICU are now increasingly required to leave the ICU to assess and assist in the management of patients on general wards. A distinction could perhaps be made between intensive care (ie, treatment within the ICU) and critical care (ie, intensive treatment, extending to other parts of the hospital). Medical emergency or outreach teams often operate within a context of critical care without walls.[3]

Substantial local, regional, and international differences exist in the way ICUs have developed and function. In many countries, there has been a traditional separation between patients needing surgical and medical treatment; in the USA, such separation is still common, but is mainly a historical distinction. Patients in medical and surgical ICUs have similar problems (eg, infection, cardiorespiratory instability, fluid imbalance, metabolic complications); the main difference is that patients in medical ICUs have much higher mortality rates[4,5] because surgery is often a curative procedure. Nevertheless, separation might continue for financial or management reasons since surgical and medical departments are often separated within hospitals. Importantly, irrespective of the initiating insult, such as infection, trauma, or haemorrhage, the final common pathway for many patients in the ICU (ie, multiple organ failure) is similar. Panel 1 lists some of the arguments for and against separation of ICUs into separate surgical and medical units.

Search strategy and selection criteria

Relevant literature published in English was selected from Medline since its inception, and our personal databases and personal knowledge of developments in the specialty of intensive care gathered from more than 50 years of combined experience in this specialty. We largely selected publications in the past 5–10 years, but did not exclude commonly referenced and highly regarded older publications.

***Panel 1:* Advantages and disadvantages of separate medical and surgical intensive care units (ICUs)**

Advantages

- Can be easier in terms of finances since surgical and medical hospital budgets are often separate
- Encourages development of specialised skills and knowledge by medical and nursing staff for the specific clinical domain
- More homogeneous groups of patients, helping diagnosis
- Convenience—eg, surgical ICU could be located near operating theatres

Disadvantages

- Intensive care medicine is the same irrespective of the original cause of illness
- Increased costs as more equipment is needed
- Increased staffing needs
- Reduced ability to care for critically ill patients who do not fit into the usual category
- Might increase burnout in the ICU

Evidence-based medicine and progress

The history of intensive care medicine is one of small steps in progress related largely to developments in technology. A good analogy can be made to the motor industry that also developed slowly with every new innovation. For example, improved patient and ventilator interfaces enable mechanical ventilation to be better tolerated, allowing reduced use of sedative drugs and helping the weaning process. Large, clumsy ventilators have gradually been replaced by small, user-friendly, and often portable models. The same can be said for monitoring equipment, renal support systems, and most other items of equipment used within the ICU setting.

Progress in the introduction of specific therapeutic interventions has been less apparent than the advances made in monitoring and organ support devices. This difference is partly related to the complexity of the disease processes; difficulties with definitions and diagnosis; heterogeneity of the population in intensive care; and subsequent variations in interpretation, acceptance, and thus implementation of study findings.

Evidence-based medicine should form the basis for all management decisions in all specialties of medicine. However, the quality of the available evidence in intensive care medicine, and its relevance to an individual patient, is still arguably less than in many other specialties. An impressive, and perhaps unmatched, achievement of the specialty has been the proliferation of local, national, and international academic research networks that organise multicentre trials or gather large amounts of data to inform practice and outcomes. Many studies from such groups have been published in general, high-impact-factor journals in the past two decades. Nevertheless, randomised controlled trials are difficult to undertake in the broad mix of conditions and patients within intensive care, particularly when large numbers have to be enrolled to detect small differences in survival. Thus, for example, notable success has been achieved from early induced hypothermia after cardiac arrest secondary to ventricular arrhythmias, but the answer is not as clear cut after other acute cerebral insults such as traumatic brain injury or stroke.[6] The heterogeneity factor can even apply to single disorders such as sepsis, a catch-all syndrome that includes several clinical disorders but in which the timing and extent of any therapeutic immunomodulation might be crucial to outcome.[7] The effect of any new intervention is also further confounded and complicated by wide variability in the management regimens that are concurrently applied—eg, related to sedation, nutrition, blood product transfusion, fluid balance, and haemodynamic endpoints.

Whereas some patients might improve with an intervention, others might not, or could even be harmed, such that an overall trial result could be negative. Results of most of the reported randomised controlled trials in intensive care have been negative,[8] with some even showing overall harm from theoretically advantageous interventions (table 1).[9–13] Therefore, our understanding of the underlying pathophysiological changes of critical illness, and the lack of diagnostic methods to rapidly identify suitable patients and appropriate timing for immunomodulatory or other therapies is still far from perfect.

The lack of a strong evidence base for many intensive-care interventions and treatments is clearly evident in the guidelines provided by the Surviving Sepsis Campaign for the management of severe sepsis.[14,15] The aim of this initiative, developed in 2002, was to improve the global management, diagnosis, and treatment of sepsis through the development and implementation of evidence-based guidelines. The first iteration, generated by a group of about 50 international experts in critical care and infectious diseases using a modified Delphi method, was reported in 2004,[14] with a revision in 2008.[15]

	Intervention	Outcome
Takala et al[9]	Growth hormone treatment in patients needing at least 10 days of treatment in intensive care	Increase in hospital mortality rate
Lopez et al[10]	Nitric oxide synthase inhibition in patients with septic shock	Increase in 28-day mortality rate
Esteban et al[11]	Non-invasive positive pressure ventilation for patients with respiratory failure after extubation	Increased mortality rate in intensive care unit
Brunkhorst et al[12]	Two-by-two factorial design in patients with severe sepsis receiving either intensive insulin therapy or conventional insulin therapy, and either 10% pentastarch or modified Ringer's lactate for fluid resuscitation	Doubling of serious adverse events with intensive insulin therapy and increased rates of acute renal failure and renal replacement therapy with the starch solution
NICE-SUGAR[13]	Intensive glucose control (target blood glucose range 4·5–6·0 mmol/L) versus conventional glucose control (target range ≤10·0 mmol/L) in patients in intensive care	Increase in 90-day mortality rate

***Table 1:* Examples of interventions shown to worsen outcomes in randomised controlled trials**

www.thelancet.com Published online October 9, 2010 DOI:10.1016/S0140-6736(10)60575-2

	Intervention	Outcome
ARDS-Net Tidal Volume study[18]	Reduction in plateau pressures (and tidal volumes) for mechanical ventilation in patients with acute lung injury or acute respiratory distress syndrome	Reduction in hospital mortality rate
TRICC[19]	Reduction in trigger for blood transfusion (haemoglobin of 70 g/L *vs* 90 g/L)	No change overall, but mortality rate was lower in subsets of less acutely ill patients (APACHE score ≤20) or those younger than 55 years compared with patients with APACHE score greater than 20 or age greater than 55 years, respectively
Hypothermia after Cardiac Arrest Study Group;[20] Bernard et al[21]	Hypothermia after ventricular fibrillation-related cardiac arrest	Improved neurological outcomes and reduced mortality
Kress et al[22]	Daily hold of sedation in patients	Reduced duration of mechanical ventilation and stay in intensive care unit

APACHE=acute physiology and chronic health evaluation.

Table 2: **Examples of interventions shown to improve outcomes that have generally become incorporated into mainstream practice**

Guidelines were provided for all aspects of management, including initial resuscitation, diagnosis, antibiotics, and source control; fluid and vasoactive drug therapy; adjuncts such as steroids and drotrecogin alfa (activated protein C); general aspects such as administration of blood products, mechanical ventilation, and glucose control; and considerations for limitation of support that will extend life. Recommendations, graded according to the level of evidence available, were developed for every category. However, only a few of these recommendations could be supported by high-quality evidence from randomised controlled trials or meta-analyses.[16] Hence, even though findings of recent studies, such as the one done by Ferrer and colleagues,[17] indicate that compliance rates can be improved with educational programmes, many of these recommendations are rather ambiguous and the physician has to choose from several options—eg, type of fluid resuscitation, type of vasopressor agent, and when to prescribe corticosteroids or activated protein C.

Although results of some randomised controlled trials have been successfully incorporated into mainstream practice (table 2),[18–22] uncertainty about the generalisability of study results, perceptions of potential harm, and applicability to individual patients has often led to poor uptake of interventions, even those shown to be beneficial in randomised controlled trials or meta-analyses (table 3).[23–32] Examples include the use of selective digestive decontamination for the prevention of nosocomial infection,[25,31] administration of γ globulin in severe sepsis,[27–29] and perioperative circulatory optimisation.[26,32] Moreover, results of many other studies that show an improvement in outcome have been challenged, with confidence and belief dissipated by the findings of subsequent trials that do not confirm initial results. Striking instances include the use of gastric tonometry to guide therapy in sepsis,[23,33] tight glycaemic control,[12,13,34] and the use of activated protein C in patients with severe sepsis.[24] In the case of activated protein C, an overall beneficial effect was noted for survival,[24] yet, on the basis of results from subsequent studies in different populations,[35,36] and registry data, the European Medicines Agency has mandated another placebo-controlled randomised controlled trial (number NCT00604214, registered with ClinicalTrials.gov). Panel 2 summarises the history of activated protein C so far.[40,43–46]

	Intervention	Outcome
De Smet et al,[31] de Jonge et al[25]	Selective gut decontamination	Reduction in 28-day, intensive care unit, and hospital mortality rates
Kreymann et al,[27] Turgeon et al,[28] Laupland et al[29]	Immunoglobulins for patients with severe sepsis	Reduction in mortality rate
PROWESS[24]	Drotrecogin alfa (activated protein C) for severe sepsis	Reduction in 28-day mortality rate
Pontes-Arruda et al[30]	Diet enriched with eicosapentaenoic acid or gamma-linolenic acid in mechanically ventilated patients with acute lung injury or acute respiratory distress syndrome	Reduction in mortality rate, time spent in an intensive care unit, and duration of mechanical ventilation
Gutierrez et al[23]	Use of gastric tonometric measurement of gastric mucosal pH to titrate fluid and inotrope therapy	Improved hospital survival in a subset of patients with normal gastric mucosal pH on admission to intensive care unit

Table 3: **Examples of interventions shown to improve outcomes in randomised, controlled trials (or meta-analyses) but have not become routinely incorporated into standard practice**

Paradoxically, the major contribution of randomised controlled trials in critical care settings has been the finding that overtreatment is often harmful. Excessive blood transfusion,[19] targeting supranormal cardiac output and oxygen delivery values,[48] high tidal volumes in mechanically ventilated patients,[18] excessive calorie intake,[49] and excess sedation[22,50] have all been associated with worse outcomes. Use of more conservative or less invasive therapies often represents the best approach—eg, increased use of non-invasive mechanical ventilatory techniques. This philosophy is also likely to be increasingly applied in the future as established practices and use of drugs—eg, sedative agents,[51] proton-pump inhibitors,[52] and catecholamines[53]—are specifically challenged.

***Panel 2:* Controversy about drotrecogin alfa (activated protein C)**

Activated protein C was the first immunomodulator that significantly reduced the mortality rate in patients with severe sepsis in a randomised controlled trial.[24] The pivotal phase III trial (PROWESS)[24] was stopped early after enrolment of 1690 (850 treatment, 840 control) of a planned 2280 patients when an interim analysis showed significant 28-day mortality benefit in patients treated with activated protein C (absolute reduction 6·1%, relative reduction 19·4% (95% CI 6·6 to 30·5). However, the results of a post-hoc analysis suggested that benefit occurred mainly in the severely ill with, worryingly, increased harm in mild cases through unknown mechanisms. The US Food and Drugs Administration and the European Medicines Agency (EMEA) took the pragmatic step of granting registration approval for use only in severely ill patients, but mandated several follow-up studies to investigate some of these issues. Crucially, they did not request a second pivotal randomised controlled trial, which is routine with new drugs.

On launch, this drug attracted immediate controversy[37–39] because of issues relating to protocol changes during the trial, cost (about £7000 per course of treatment), potential bleeding complications, and criticisms of undue industry influence. Detractors and supporters argued robustly, and results of subsequent studies and registry data[35,36] did not resolve this continued debate. Notably, different countries responded differently in terms of uptake, even among western European countries.[40] In 2007, the EMEA requested that another pivotal phase III trial be done to further elucidate the efficacy of activated protein C. PROWESS-SHOCK is now in progress. Additionally, titration of dose and duration according to plasma concentrations of protein C and pharmacogenomic data to identify patients who are potentially more likely to benefit from the drug are being investigated in other studies.

Evidence for use of activated protein C

- Results of a multicentre, prospective randomised controlled trial have shown overall outcome benefit[24]
- Findings of an open-label study[41] and registry data[42] have suggested improved outcomes
- Several mechanisms have been described, including immunomodulation (eg, antagonistic to nuclear factor-κB,[40] endothelial protection,[43] reduced thrombin generation,[40] protease-activated receptor-1 agonism,[44] and downregulation of nitric oxide synthase and angiotensin II systems[44]
- Demonstration of microcirculatory improvements[45]
- Outcome benefit was greater in patients with more severe coagulopathy[46]

Evidence against use of activated protein C

- Benefit mainly noted in cohort of patients who were severely ill (acute physiology and chronic health evaluation [APACHE] II score ≥24 or at least two organ failures)[24,47]
- No benefit and, in some cases, harm (eg, single-organ failure after surgery) in patients with low-mortality risk in a further prospective randomised controlled trial[35]
- No benefit was noted in a prospective randomised controlled trial in paediatric patients[36]
- No significant mortality benefit was noted in long-term outcomes[47]
- Only one large prospective randomised controlled trial has been done so far with criticisms about changes in protocol and drug preparation[37]
- Criticisms of manufacturer's marketing campaigns[38]
- Main role in improvement of sepsis outcomes is still not known
- Risk of bleeding seems to be higher in general usage than in study populations[39]

Process of care

Improved outcomes have been achieved with general improvements in the process of care rather than the use of specific therapeutic interventions.[54] These improvements, often through patient safety and quality initiatives,[55] include increased attention to detail; prompt recognition and intervention for cardiorespiratory deterioration and infection; prevention of avoidable complications such as nosocomial infection, joint contractures, and pressure sores; early mobilisation;[56] and frequent rereview of the patient.[57] The use of local, national, or international guidelines, and written or mental checklists, such as FASTHUG (panel 3),[58] encourages regular assessment of important aspects of the care of all critically ill patients and enables treatments to be applied systematically, potentially improving outcomes.[59] Increased widespread use of electronic monitoring and support has probably also helped to prevent errors and improve outcomes.[60] The importance of a multidisciplinary approach in improvement of patient care is universally accepted. Specialist input from nutritionists, physiotherapists,[56] respiratory therapists, pharmacists,[61] and others provides invaluable support to the ICU team. A full-time intensivist service is also important for improvement of outcomes; as shown in a systematic review by Pronovost and colleagues,[62] ICUs with high-intensity intensivist staffing (mandatory consultation or all care directed by intensivists) had reduced hospital mortality rates in 16 (94%) of 17 studies, resulting in a pooled estimate of the relative risk of 0·71 (95% CI 0·62–0·82).

Increasingly, intensive care practitioners are taking their specific skills outside the physical ICU structure, not only to the general ward, with outreach or medical emergency teams assisting early identification and management of critical disease processes and monitoring the progress of patients recently discharged from the ICU, but also, in some hospitals, to follow-up clinics. Awareness of the many physical and psychological ramifications of critical illness that can continue for months or even years after discharge (eg, neuromyopathies, various psychiatric and cognitive syndromes, and postextubation airway problems)[63–65] draws attention to the importance of continued specialist involvement in the holistic care of ICU survivors and their families.[66,67]

Future challenges and opportunities

So what does the future hold for intensive care medicine? We envisage major challenges and exciting opportunities in several aspects. As the population ages and health-care expectations increase, the numbers of patients needing intensive care, with the associated increasing costs, will add a substantial burden on an already overstretched service. Some further productivity might be gained through reductions in patient stay from early recognition and prevention of organ failure, and efficiencies might be improved through changes in staffing patterns and use of electronic supports. However, as labour costs dominate the ICU budget, a substantial challenge is to make savings and increase throughput without greatly affecting the quality of care offered. Governments and society need to establish how much critical care they can afford, rather than simply placing an unreasonable responsibility on the intensivist to make decisions about rationing. Importantly too, there are huge predicted

***Panel 3:* Seven components of FASTHUG[58] that should be assessed every time a patient is seen by a member of the intensive care unit (ICU) team**

Feeding
- Can the patient be fed orally? If they cannot be fed orally, should enteral or parenteral feeding be started? Is caloric intake adequate?

Analgesia
- Is the patient receiving adequate, but not excessive, analgesia?

Sedation
- Is the patient not receiving too much sedation?

Thromboembolic prevention
- Should the patient be receiving low-molecular-weight heparin or mechanical adjuncts?

Head of the bed elevated
- Is the head of the bed in the optimum position at 30–45° (unless contraindicated, eg, threatened cerebral perfusion pressure)

Ulcer prophylaxis
- Is prophylaxis for stress ulcer indicated?

Glucose control
- Is glucose control being maintained within the limits defined in the ICU?

shortfalls in ICU staffing,[68] presenting extra challenges for the organisation and function of the ICU. Telemedicine might assist small units that cannot provide 24-h specialist cover, and is likely to be used more often in ICUs of the future.[69] Strategies are needed to encourage doctors, nurses, and other allied health-care professionals to move into intensive care, and to improve training schemes. Because of the increasing pressures mentioned above, and the increased awareness that outcomes greatly improve if deterioration in organ function can be ameliorated or even avoided in the first place, more emphasis will need to be placed on prevention of critical illness. This prevention can be achieved through early identification and improved management of high-risk patients in the settings of prehospital, emergency department,[70] general ward, and operating theatre,[26] though this does require adequate training and motivation of all medical and allied staff. An increased availability of intermediate care units, in which patients can be offered more support and monitoring than they receive on a general ward, yet less than they would receive in an intensive care unit, might help this process. Although such availability would constitute a further cost pressure, savings made through prevention of critical illness could offset this expenditure.

The increasing likelihood of pandemics and major natural and terrorist disasters could also place extreme demands on the adequate provision of critical care. Policies need to be in place to cope with an influx of large numbers of critically ill or injured patients, and the possible need to triage those likely to die.[71,72]

Difficulties with clinical trial design and conduct remain. We often enrol heterogeneous populations of critically ill patients, such as those with sepsis or acute respiratory distress syndrome, and then add a severity score (eg, acute physiology and chronic health evaluation [APACHE], simplified acute physiology score) to characterise how sick they are. The benefits with activated protein C and corticosteroids were predominantly noted in the sickest patients[24,73] however, the best method of assessment of disease severity is not known. Scoring systems for disease severity, such as APACHE II, are often used, but were not designed for this purpose and might lead to incorrect classification of patients.[74] Another approach to the design of randomised controlled trials is to undertake studies in specific groups—eg, patients with meningococcaemia, but such studies will result in slow enrolment if done in one or a few centres, or might add too much centre heterogeneity if too many participate from different countries and regions. Perhaps a better approach in the future will be to use techniques that allow patients to be characterised into appropriate subgroups. For example, the definition of acute respiratory distress syndrome might be improved not so much by the degree of hypoxaemia (which can depend on several ventilator characteristics), but by the degree of fibroproliferation in bronchoalveolar lavage fluid.[75] Similarly, sepsis and the extent of the inflammatory response will be better characterised by use of one or a combination of biomarkers than by use of the degree of fever or the white blood cell count.[76] Improved understanding of the underlying metabolic and cellular derangements in these disease processes will help establish how best to characterise affected patients, and could help target therapies to patients who are most likely to benefit.

The continued rise in infection rates related to widespread use of aggressive surgical techniques and immunosuppressive therapies in an increasingly ageing population is an increasing cause for concern. Additionally, there is an inexorable rise in antibiotic resistance, yet there are few new antibiotics in the pipeline, particularly for gram-negative organisms. Encouragingly, however, improved diagnostic tests will help early identification of the presence of infection, the causative microorganism and its resistance pattern; they will also support clinical decision making to rationalise or discontinue antibiotic therapy.[77] In combination with improved, evidence-based infection-control regimens that reduce the incidence of nosocomial infection, antibiotic requirements should also diminish. This reduction should affect development of antibiotic resistance but also requires increased responsibility on the part of physicians prescribing the antibiotics.

Time and mode of death are steadily changing. Most patients who now die in the ICU do so after the development of multiple organ failure. Improved strategies to prevent multiple organ failure and hasten recovery processes are urgently needed. The management of multiple organ failure consists mainly of organ support, with the exception of antibiotic therapy and source removal in patients with sepsis. Thus, the respiratory system is supported by mechanical ventilation, the kidneys are supported by extracorporeal support, the cardiovascular system is supported by vasoactive and inotropic drugs, and so forth. However, there is little evidence that any of this organ support is, in itself, curative. Use of these techniques is mainly to support the patient during the period of illness in the hope that extra time will enable the patient to self-heal. This theory is supported by some suggestions that cells should be allowed to rest or hibernate to allow recovery.[78] One good example of this self-healing is the use of hypothermia after cardiac arrest to rest the brain.[6,20,21] In the future, we need to target the treatment of patients in the ICU according to their risk of developing multiple organ failure. For such targeting to be effective, timing will be crucial. First, methods to protect the organs need to be developed that can be administered before organ failure has become established; these might include strategies to restrict tissue hypoxia, reduce an excessive inflammatory response, or protect against oxidant damage. Second, if multiple organ failure is already established, the cells might need to be rested. Potential strategies include hypothermia or suspended animation by use of hydrogen sulphide.[79] Third, techniques for stimulation of recovery processes, perhaps through mitochondrial biogenesis,[80] need to be considered. Clearly, all these aspects need further study but if approaches could be established that reduce the development of cellular and, hence, organ failure, or enhance cellular recovery, such strategies would constitute a major advance for all critically ill patients.

Conclusion

The ICU is playing an increasingly important part within the hospital, and ICU staff have a higher profile in hospital-wide acute care. Improvements in understanding the basic cellular mechanisms underlying critical illness, ICU management and structure, and critical care trial design, alongside continued advances in technology, diagnostic tests, and therapies, will help to create real progress in terms of patient outcomes.

Contributors

J-LV drafted the initial report that was subsequently revised by both authors.

Conflicts of interest

J-LV has served as a paid consultant for Eli Lilly, Eisai, and GlaxoSmithKline; participated in clinical trials sponsored by Eisai, Eli Lilly, Artisan, and Astellas; and been an invited speaker at conferences supported by Eli Lilly, Esai, and GlaxoSmithKline. MS has served as a consultant to, and has been an invited speaker at conferences supported by, Eli Lilly and Deltex Medical. Additionally, Deltex Medical provides a yearly unrestricted donation to MS's research fund at University College London.

Acknowledgments

University College London Hospital/University College London receives support from the UK Department of Health's National Institute for Health Research Comprehensive Biomedical Research Centre funding scheme.

References

1 Escarce JJ, Kelley MA. Admission source to the medical intensive care unit predicts hospital death independent of APACHE II score. *JAMA* 1990; **264:** 2389–94.
2 Flabouris A, Hart GK, George C. Outcomes of patients admitted to tertiary intensive care units after interhospital transfer: comparison with patients admitted from emergency departments. *Crit Care Resusc* 2008; **10:** 97–105.
3 Hillman K. Critical care without walls. *Curr Opin Crit Care* 2002; **8:** 594–99.
4 Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34:** 344–53.
5 Moran JL, Bristow P, Solomon PJ, George C, Hart GK. Mortality and length-of-stay outcomes, 1993–2003, in the binational Australian and New Zealand intensive care adult patient database. *Crit Care Med* 2008; **36:** 46–61.
6 Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008; **371:** 1955–69.
7 Marshall JC. Sepsis: rethinking the approach to clinical research. *J Leukoc Biol* 2008; **83:** 471–82.
8 Ospina-Tascon GA, Buchele GL, Vincent JL. Multicenter, randomized, controlled trials evaluating mortality in intensive care: doomed to fail? *Crit Care Med* 2008; **36:** 1311–22.
9 Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; **341:** 785–92.
10 Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med* 2004; **32:** 21–30.
11 Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; **350:** 2452–60.
12 Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358:** 125–39.
13 Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360:** 1283–97.
14 Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; **32:** 858–73.
15 Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; **36:** 296–327.
16 Vincent JL. Is the current management of severe sepsis and septic shock really evidence based? *PLoS Med* 2006; **3:** e346.
17 Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA* 2008; **299:** 2294–303.
18 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342:** 1301–08.
19 Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340:** 409–17.
20 Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346:** 549–56.
21 Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346:** 557–63.
22 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; **342:** 1471–77.

23 Gutierrez G, Palizas F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339:** 195–99.

24 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344:** 699–709.

25 de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet* 2003; **362:** 1011–16.

26 Poeze M, Greve JW, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. *Crit Care* 2005; **9:** R771–79.

27 Kreymann KG, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; **35:** 2677–85.

28 Turgeon AF, Hutton B, Fergusson DA, et al. Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; **146:** 193–203.

29 Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. *Crit Care Med* 2007; **35:** 2686–92.

30 Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *JPEN J Parenter Enteral Nutr* 2008; **32:** 596–605.

31 de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; **360:** 20–31.

32 Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; **37:** 2079–90.

33 Gomersall CD, Joynt GM, Freebairn RC, Hung V, Buckley TA, Oh TE. Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial. *Crit Care Med* 2000; **28:** 607–14.

34 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; **345:** 1359–67.

35 Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa [activated] for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; **353:** 1332–41.

36 Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007; **369:** 836–43.

37 Mackenzie AF. Activated protein C: do more survive? *Intensive Care Med* 2005; **31:** 1624–26.

38 Eichacker PQ, Natanson C, Danner RL. Surviving sepsis—practice guidelines, marketing campaigns, and Eli Lilly. *N Engl J Med* 2006; **355:** 1640–42.

39 Eichacker PQ, Natanson C. Increasing evidence that the risks of rhAPC may outweigh its benefits. *Intensive Care Med* 2007; **33:** 396–99.

40 Joyce DE, Gelbert L, Ciaccia A, DeHoff B, Grinnell BW. Gene expression profile of antithrombotic protein c defines new mechanisms modulating inflammation and apoptosis. *J Biol Chem* 2001; **276:** 11199–203.

41 Vincent JL, Bernard GR, Beale R, et al. Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; **33:** 2266–77.

42 Martin G, Brunkhorst FM, Janes JM, et al. The international PROGRESS registry of patients with severe sepsis: drotrecogin alfa (activated) use and patient outcomes. *Crit Care* 2009; **13:** R103.

43 Joyce DE, Nelson DR, Grinnell BW. Leukocyte and endothelial cell interactions in sepsis: relevance of the protein C pathway. *Crit Care Med* 2004; **32:** S280–S286.

44 Gupta A, Gerlitz B, Richardson MA, et al. Distinct functions of activated protein C differentially attenuate acute kidney injury. *J Am Soc Nephrol* 2009; **20:** 267–77.

45 De Backer D, Verdant C, Chierego M, Koch M, Gullo A, Vincent JL. Effects of drotrecogin alfa activated on microcirculatory alterations in patients with severe sepsis. *Crit Care Med* 2006; **34:** 1918–24.

46 Dhainaut JF, Yan SB, Joyce DE, et al. Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004; **2:** 1924–33.

47 Angus DC, Laterre PF, Helterbrand J, et al. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. *Crit Care Med* 2004; **32:** 2199–206.

48 Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330:** 1717–22.

49 The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; **325:** 525–32.

50 Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; **371:** 126–34.

51 Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine *vs* midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301:** 489–99.

52 Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; **301:** 2120–28.

53 Singer M. Catecholamine treatment for shock—equally good or bad? *Lancet* 2007; **370:** 636–37.

54 Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* 2008; **133:** 1120–27.

55 Pronovost P, Holzmueller CG, Needham DM, et al. How will we know patients are safer? An organization-wide approach to measuring and improving safety. *Crit Care Med* 2006; **34:** 1988–95.

56 Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; **373:** 1874–82.

57 Pronovost PJ, Jenckes MW, Dorman T, et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA* 1999; **281:** 1310–17.

58 Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med* 2005; **33:** 1225–29.

59 Papadimos TJ, Hensley SJ, Duggan JM, et al. Implementation of the "FASTHUG" concept decreases the incidence of ventilator-associated pneumonia in a surgical intensive care unit. *Patient Saf Surg* 2008; **2:** 3.

60 Shulman R, Singer M, Goldstone J, Bellingan G. Medication errors: a prospective cohort study of hand-written and computerised physician order entry in the intensive care unit. *Crit Care* 2005; **9:** R516–21.

61 MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Crit Care Med* 2008; **36:** 3184–89.

62 Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002; **288:** 2151–62.

63 Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; **174:** 538–44.

64 Jackson JC, Mitchell N, Hopkins RO. Cognitive functioning, mental health, and quality of life in ICU survivors: an overview. *Crit Care Clin* 2009; **25:** 615–28.

65 Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. *Crit Care* 2010; **14:** R6.

66 Griffiths RD, Jones C. Seven lessons from 20 years of follow-up of intensive care unit survivors. *Curr Opin Crit Care* 2007; **13:** 508–13.

67 Tan T, Brett SJ, Stokes T. Rehabilitation after critical illness: summary of NICE guidance. *BMJ* 2009; **338:** b822.

68 Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA* 2000; **284:** 2762–70.

69 Breslow MJ, Rosenfeld BA, Doerfler M, et al. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Crit Care Med* 2004; **32:** 31–38.

70 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345:** 1368–77.

71 Rubinson L, Hick JL, Hanfling DG, et al. Definitive care for the critically ill during a disaster: a framework for optimizing critical care surge capacity: from a Task Force for Mass Critical Care summit meeting, Chicago, IL, USA, Jan 26–27, 2007. *Chest* 2008; **133:** 18S–31S.

72 Matzo M, Wilkinson A, Lynn J, Gatto M, Phillips S. Palliative care considerations in mass casualty events with scarce resources. *Biosecur Bioterror* 2009; **7:** 199–210.

73 Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358:** 111–24.

74 Vincent JL, Opal SM, Marshall JC. Ten reasons why we should not use severity scores as entry criteria for clinical trials or in our treatment decisions. *Crit Care Med* 2010; **38:** 283–87.

75 Armstrong L, Thickett DR, Mansell JP, et al. Changes in collagen turnover in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **160:** 1910–15.

76 Marshall JC, Reinhart K. Biomarkers of sepsis. *Crit Care Med* 2009; **37:** 2290–98.

77 Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med* 2008; **177:** 498–505.

78 Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; **364:** 545–48.

79 Wagner F, Asfar P, Calzia E, Radermacher P, Szabo C. Bench-to-bedside review: Hydrogen sulfide—the third gaseous transmitter: applications for critical care. *Crit Care* 2009; **13:** 213.

80 Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. *Crit Care* 2006; **10:** 228.