

 **Critical Care 3**

Critical care: advances and future perspectives

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This is the third in a [Series](#) of three papers about critical care

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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.

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.

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

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

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 Guidelines were provided for all aspects of management, including initial resuscitation, diagnosis, antibiotics,

	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

	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

	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 ³²	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

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}

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 catecholamines⁵³—are specifically challenged.

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

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 Drug Administration and the European Medicines Agency (EMA) 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 EMA 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 benefit²⁴
- Findings of an open-label study⁴¹ and registry data⁴² have suggested improved outcomes
- Several mechanisms have been described, including immunomodulation (eg, antagonistic to nuclear factor- κ B,⁴⁰ endothelial protection,⁴³ reduced thrombin generation,⁴⁰ protease-activated receptor-1 agonism,⁴⁴ and downregulation of nitric oxide synthase and angiotensin II systems⁴⁴)
- Demonstration of microcirculatory improvements⁴⁵
- Outcome benefit was greater in patients with more severe coagulopathy⁴⁶

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 trial³⁵
- No benefit was noted in a prospective randomised controlled trial in paediatric patients³⁶
- No significant mortality benefit was noted in long-term outcomes⁴⁷
- Only one large prospective randomised controlled trial has been done so far with criticisms about changes in protocol and drug preparation³⁷
- Criticisms of manufacturer's marketing campaigns³⁸
- Main role in improvement of sepsis outcomes is still not known
- Risk of bleeding seems to be higher in general usage than in study populations³⁹

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 FASTHUG⁵⁸ 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 increasingly 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, Eisai, 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.

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