CRITICAL CARE IN THE GLOBAL CONTEXT

It is certain that critically ill patients will be impacted by the current global financial crisis. Healthcare spending in the U.S. remains the greatest of all the world’s nations—now topping 16% of the gross domestic product, or just over two trillion U.S. dollars (1). Care of the critically ill is expensive, consuming upwards of 1% of the entire North American GDP. The U.S. presidential election recognized both the expense of health care and the disparities in delivering such care. Such disparities were found to be strongly associated with inequalities in socioeconomic status in Western European countries, and this is undoubtedly true in North America as well (2). The Obama-Biden healthcare plan aims to increase affordable coverage to Americans, in part, through a proposed National Health Insurance Exchange that will facilitate coverage among the currently uninsured (3); however, the impact of the current U.S. and global financial crisis on implementation of such a plan is uncertain (4). It is likely that over the next years, U.S. federal and state funding may fall, institutional endowments and donations will shrink, and hospital and department budgets may be cut. However, the U.S. accounts for approximately one-third of the gross world product and hence has more resources than any place else on earth with which to weather this crisis.

The developing world faces a far greater threat—that an inward economic focus of the world’s rich countries will reduce aid and interrupt debt cancellation. Even in better financial times, there is debate about whether allocation of resources to critical care services represents the best use of healthcare dollars. In the developed world, there is no standard definition of “critical care,” and no recommendations about optimal supply of critical care (5); the number of intensive care unit (ICU) beds ranges from 3 (in the UK) to 24 (in Germany) per 100,000 population. In the developing world, the debate on the value of critical care is more fierce in that competing interests of poverty and basic healthcare are compelling arguments against spending for those who are critically ill or in need of procedural or surgical care (1, 6). Although it is a perpetual national issue, it is likely that over the next years, U.S. federal and state funding may fall, institutional endowments and donations will shrink, and hospital and department budgets may be cut. However, the U.S. accounts for approximately one-third of the gross world product and hence has more resources than any place else on earth with which to weather this crisis.

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esophageal–pressure-guided PEEP management improves oxygenation (25, 26). The potential benefits of therapies based on these observations are unknown but will surely be tested. One large cohort study suggested that intensivists worsen mortality; however, most patients in the study cared for by intensivists were not cared for in intensivist-led ICUs and no mechanism for the observed harm was identified (27, 28).

Finally, some old ideas, when combined, yield impressive results. A protocol combining daily interruption of sedation and spontaneous breathing trials not only reduced duration of mechanical ventilation but appeared to have an as yet unexplained effect on long-term mortality (29). The Surviving Sepsis bundle of interventions for severe sepsis saved one life for every 23 patients cared for in a multicenter quality improvement project in Spain (30).

ACUTE LUNG INJURY AND MECHANICAL VENTILATION

Cellular and Molecular Mechanisms

A number of intriguing discoveries about the pathogenesis of lung injury were reported in 2008. Viral pathogens, such as the severe acute respiratory syndrome and influenza viruses, were shown to induce lung injury by generating oxidized phospholipids that bind toll-like receptor (TLR)4 and initiate the inflammatory response (31). Along the same lines, TLR3 was found to contribute to acute lung injury (ALI) in mice exposed to high concentrations of oxygen (32).

Polymorphisms in the myosin light chain kinase gene were found to be associated with the development of lung injury after trauma (33); mechanistically, another study found a novel role for myosin light chain kinase as a regulator of neutrophil immigration to the lung in a mouse model of sepsis-induced lung injury (34).

Other molecules that were investigated in various mouse models of ALI included the insulin-like growth factor-1 receptor (35), caveolin-1 (36), and the receptor for advanced glycation end-products (37). Chang and colleagues performed proteomic and computational analyses on bronchoalveolar lavage fluid from patients with ARDS to identify proteins enriched in ARDS and to identify potential protein–protein interactions that might be important for pathogenesis or prognosis of lung injury (38).

Mouse models of ventilator-induced lung injury implicated the adenosine receptor A2BAR as being protective (39) and the cytokine pre–B-cell colony–enhancing factor as being harmful (40). Immunomodulatory effects of surfactant proteins were described (41, 42). Hoetzl and colleagues elucidated the molecular mechanisms by which low-dose carbon monoxide protects against ventilator-induced lung injury in mice (43).

Diagnosis, Imaging, and Physiology

An important study by Levitt and colleagues demonstrated that B-type natriuretic peptide (BNP) levels could not distinguish cardiogenic from noncardiogenic pulmonary edema compared with an adjudicated blinded diagnosis by experts (44). However, BNP levels are associated with mortality in patients with ALI and sickle chest syndrome, perhaps not surprisingly as they reflect concomitant pulmonary hypertension and cardiac dysfunction (45, 46).

The use of extravascular lung water measurements may be more accurate and reliable when, similar to tidal volume, they are indexed to predicted rather than to measured body weight (47). Diffuse uptake of 18-fluorodeoxyglucose by positron emission tomography may be an early indicator of ALI in patients at risk (48). Pulmonary ultrasound may be useful in distinguishing cardiogenic from noncardiogenic edema (49).

Venous admixture does not appear to correlate well with anatomic shunt estimated by nonaerated lung on computed tomography in patients with ALI (50). The prognostic value of dead space measurements in patients with ALI was confirmed and extended, although the measured dead space may be a manifestation of shunt and exacerbated by metabolic acidosis (51, 52). Sophisticated computer models of gas exchange in ALI demonstrate that the $P_{A_{O2}}/F_{I_{O2}}$ ratio is not only $F_{I_{O2}}$ dependent, but dependent on changes in hemoglobin, $P_{aCO_2}$, and oxygen consumption (52).

Transfusion-related ALI

Transfusion-related acute lung injury (TRALI) remains an area of intense investigation. Alloimmunization from pregnancy or a previous transfusion leading to the transmission of even small amounts of donor plasma with antibodies that react to the recipient's neutrophils remains a primary hypothesis for the etiology of TRALI, and eliminating these donors is a principal approach to prevention (53–55). Reminding us that ALI is a heterogeneous syndrome with multiple pathologic presentations is the interesting pair of case reports of patients with “rapidly fatal TRALI” that did not show diffuse alveolar damage, interstitial inflammation, or intraalveolar granulocyte infiltration (56). Leukoreduction of blood did not appear to reduce the risk of ALI in a randomized trial of trauma patients, whereas eliminating women from plasma donors appeared to reduce the risk of ALI by almost 50% in a before–after analysis of ruptured abdominal aortic aneurysm cases (57, 58). Like other causes of ALI (59), TRALI is frequently missed by clinicians and is ascribed to other etiologies; however, identification may be increased by automated alerts (60, 61).

Treatment of Respiratory Failure

Noninvasive mechanical ventilation is not used in all cases where the evidence supports its use (62) but appears to be an option for many patients receiving palliative care, although the goal of care may not always be clear (63).

Clinicians appear to be changing their practice in response to clinical trials on lung protective ventilation, although routine use of 6 ml/kg predicted body weight still seems difficult to achieve even at academic medical centers (64, 65). A challenging study from a major academic center documented that lung protective ventilation is frequently not delivered because physicians are unsure about the diagnosis of ALI and may not be delivered even when ordered (66). In one relatively small but well-characterized case series, breath stacking occurred frequently in patients with ALI managed with lung protective ventilation despite heavy sedation and was associated with lower prescribed tidal volumes (67). It is unknown whether occasional stacked breaths of 10 ml/kg are more injurious than consistent 8 ml/kg breaths or spontaneous breaths of 15 ml/kg. These choices are more challenging in light of the growing research that suggests that neither tidal volume nor plateau pressure are ideal indicators of lung stress or strain in individual patients (68, 69).

Three meta-analyses evaluated the effect of prone positioning on ALI and hypoxemic respiratory failure outcomes (69–71). They reached remarkably similar conclusions: that there was no observed effect on mortality, that there was no observed effect on duration of mechanical ventilation, and that the benefits of sustained proning in a more severely ill population could not be excluded. The final hypothesis is being tested in a recently completed trial (clinicaltrials.gov identifier NCT00159939). It is important for intensivists to remain vigilant for rare causes of ALI reversible with specific
treatments, including the pulmonary manifestations of the antisyntetase syndrome which, in one case report, responded to tacrolimus after high-dose corticosteroids failed (72), and idiopathic pneumonia syndrome after stem-cell transplantation which, in a case series, responded to etanercept and corticosteroids (73). Perhaps the best way to treat ALI is to prevent it: recent cohort studies identified preventable factors including delayed resuscitation and antibiotics, elevated tidal volumes, and blood product transfusion (74). Activated protein C reduced dead space but did not affect ventilator-free days or mortality in a highly selected group of nonseptic ALI patients with low mortality (75). The use of “prophylactic” levels of PEEP (5–8 cm H2O) versus zero was evaluated in 131 patients who were not hypoxia ventilated without any effect on mortality or ARDS; however, a statistically significant reduction in VAP was noted (76).

Bedside tools for monitoring lung recruitment continue to evolve, with electrical impedance tomography (which generates tomographic images based on tissue impedance rather than radiographic density) and the oxygen wash-in–wash-out technique becoming increasingly refined (77, 78). The clinical utility of these monitoring tools has not been established.

**Weaning and Tracheostomy**

Surveys from Germany and the UK document that the majority of ICU tracheostomies are performed percutaneously at the bedside by two operators using bronchoscopic guidance. Substantial variation in follow-up care and timing was noted (79, 80). A small clinical trial of early tracheostomy showed no statistical benefit in survival or duration of mechanical ventilation (81). A large cohort study suggested an explanation: the survival benefits of tracheostomy, if not a result of selection bias, were very small and will require a large trial to demonstrate (82). Extubation to noninvasive ventilation may be a viable weaning alternative in selected patients who fail spontaneous breathing trials; however, this study implemented weaning by intermittent mandatory ventilation in the control arm, which has generally been shown to be an inferior weaning approach (83). A meta-analysis of prophylactic corticosteroids in adults to prevent laryngeal edema and reintubation supported their safety and efficacy (84). The race between computer-driven and protocol- or clinician-driven weaning continues with a recent trial showing no benefit from a computer-driven system (85), but new ones are on the horizon (86). Two recent trials raise questions about the universal generalizability of recommendations for sedation protocols and for sedation interruption. In a single center trial in an Australian teaching hospital, a sedation protocol was not statistically associated with reduced duration of mechanical ventilation or any difference in the use of sedative drugs. In a challenging trial, sedation interruption was associated with excess mortality and the trial was stopped early (87).

**Describing and Changing Life after the ICU**

Hypoglycemia in the ICU was associated with depression symptoms after ALI, although the clinical implications of this are still unclear (88). Although ICU-acquired weakness was associated with poor outcome, it was not associated with corticosteroid administration in a secondary analysis of ARDS Network trial data (89). Interest in early ambulation and physical therapy of patients who are ventilator-dependent is growing ahead of data on its safety, efficacy, or generalizability to surgical, trauma, and neurosurgical populations. However, the early experience seems extremely promising (90, 91). A systematic review of psychiatric morbidity after ARDS found that the point prevalence of “clinically significant” symptoms of depression ranged from 17 to 43% (four studies) and post-traumatic stress disorder (PTSD), 21 to 35% (four studies) (92). A careful analysis of a well-described cohort of patients that documented drug dosing, objective measures of level of sedation, and post-ICU psychiatric morbidity found that patients who were the most awake and the least awake during their ICU stay had the lowest levels of symptoms consistent with PTSD (93). Similarly, a large study of adult ICU survivors soon after ICU discharge found that amnesia for the early period of critical illness was associated with PTSD-related symptoms; this finding may reflect initial disease severity rather than a particular sedation approach (94). Survivors of critical illness associated with major trauma report significant levels of sexual dysfunction (95). However, sleep disturbances in long-term ICU survivors appear related to concurrent illness rather than the ICU admission (96). Survivors of cardiac arrest without severe neurological disabilities had similar quality of life compared with other groups of patients (97). A prominent study of short-term effects of pediatric intensive care found that delusional memories are reported by almost one-third of children after ICU admission and are associated both with the duration of opiates and benzodiazepines and risk of post-traumatic stress (98).

**INFECTION PREVENTION AND SEPSIS**

**Cellular and Molecular Mechanisms**

The toll-like receptor (TLR) family, involved in recognizing pathogen-associated molecular patterns, continues to be implicated in the pathogenesis of sepsis. In a cecal ligation and perforation (CLP) model, TLR9 knockout mice were protected against peritoneal sepsis, possibly due to enhanced recruitment of dendritic cells and granulocytes to the site of infection. Administration of a TLR9-blocking peptide as long as 12 hours after CLP also improved survival (99). In another study, blockade of both TLR2 and TLR4 and concomitant antibiotic therapy improved survival in a mouse model of gram-negative sepsis compared with antibiotic therapy alone (100). A specific polymorphism in TLR1 was associated with worse outcome from sepsis and from sepsis-induced lung injury, potentially due to the polymorphism causing increased cell surface expression of the receptor and greater cytokine production (101).

Ward and colleagues continued their work on complement, identifying the complement receptor C5L2 as a functional receptor for C5a that is important in a murine model of sepsis, possibly via regulation of high mobility group box 1 (HMGB1) release (102). Another group discovered that the Ashwell receptor, the major lectin on hepatocytes, plays an unsuspected role in moderating disseminated intravascular coagulation (DIC) in pneumococcal sepsis, by clearing platelets that had been damaged (desialylated) by the pneumococcal neuraminidase (103). Insulin-like growth factor-1 (IGF-1) supplementation improved survival in a mouse model of sepsis, possibly by improving hepatic clearance of bacteria by Kuppfer cells (104). Mice deficient in the costimulatory molecules CD40 and CD80/86 exhibited improved survival in a CLP model of sepsis (105).

Two other studies shed light on fundamental processes related to sepsis. Although the clinical role of activated protein C has highlighted the connection between inflammation and coagulation in sepsis, the mechanism of this link is not well understood. Dendritic cells have now been shown to be key; signaling via protease-activated receptor 1 (PAR-1) on the dendritic cell surface, and its downstream effector sphingosine 1-phosphate, regulate the compartmentalization of inflammation.
to lymph nodes and the development of DIC (106). Another study highlighted the importance of the endothelium to the pathogenesis of sepsis. When the proinflammatory transcription factor NF-κB was inhibited selectively in endothelial cells of septic mice, multiple organ failure, DIC, and mortality were significantly attenuated. The findings were all the more remarkable given that there was no effect of NF-κB inhibition in endothelial cells on the clearance of pathogenic bacteria (107).

**Infection Prevention**

Influenza vaccination is recommended annually to patients who are at high-risk of serious illness and death. Some observational studies suggest up to a 50% mortality reduction for older patients receiving influenza vaccination, but this risk reduction may be confounded by a “healthy user” effect. A Canadian cohort study found that functional and socioeconomic status among recipients might explain some of this effect (108). The role of statins for risk reduction of infection continues to be investigated. A large population-based study from Denmark found a decreased mortality among statin users subsequently hospitalized with pneumonia, after adjustment for other factors including the propensity for statin use (109). A similar protective effect was observed after major trauma for elderly patients (110). We will learn if statins truly have a protective effect only from prospective clinical investigations.

**Ventilator-associated Pneumonia**

One study found that the use of increased PEEP in patients without hypoxia may lower the rate of VAP, or VAP detection (76). Despite reports questioning the utility of endotracheal aspirates in guiding VAP therapy, a retrospective study in one ICU demonstrated a higher rate of initial appropriate antibiotic use for VAP when results of previous aspirates were considered, in comparison to empiric American Thoracic Society guidelines (111). Two other studies found that surveillance for colonization with resistant microorganisms was predictive of subsequent infection etiology and led to improved adequacy of empiric antimicrobial treatment in patients who were critically ill (112, 113). However, in a retrospective analysis of a large randomized controlled factorial trial of empiric antibiotics and diagnostic sampling methods for suspected VAP, there was poor agreement between prior cultures and cultures performed at time of suspicion of VAP. The authors recommended that prior cultures should not be used to narrow the spectrum of empiric antibiotics (114). Post-hoc analyses of the same trial found that clinician judgment of the probability of VAP did not correlate with processes of care or clinical outcomes (115). A large clinical trial and a well-performed meta-analysis of empiric antibiotics for suspected VAP found that monotherapy is not inferior to combination therapy and that there is no clearly superior empiric regimen (116, 117).

*Pseudomonas aeruginosa* infection is a common cause of VAP, with a high attendant mortality risk, but the underlying mechanisms are unclear. Supporting the hypothesis that this may be due to failure in eradication of type III secretory system (TTSS) isolates (118), one study found that increased apoptosis in neutrophils by the TTSS (+) isolates may explain the delay in eradication of *Pseudomonas* strains in patients with VAP and postulated that short-course antimicrobial therapy may not be adequate in clearing *Pseudomonas* infection with a TTSS secretory phenotype.

Although risk factors for *Candida* infections are clearly defined (119), the importance of the *Candida* species in respiratory and systemic isolates of critically ill patients continues to be uncertain (120). A retrospective analysis of respiratory isolates in a large randomized trial found that *Candida* colonization was associated with increased hospital mortality, but a causal relationship was not clear (121). A less-well recognized pathogen in respiratory secretions, herpes simplex virus type 1, was detected more commonly in critically ill patients than community-based patients; and high loads in bronchoalveolar lavage fluid were associated with increased mortality (122).

In a 200-patient trial investigating the proposed nonantibiotic effects of clarithromycin, the active drug accelerated the resolution of VAP and weaning from mechanical ventilation in patients that survive but did not alter mortality (123).

**Sepsis and Inflammatory States**

There is an underappreciation of sepsis among the general public (124) despite its associated high attributable mortality risk and reduced health-related quality of life (125, 126). Barnato and colleagues recommend that focused interventions to improve processes and outcomes of care at hospitals that disproportionately treat patients with higher rates of sepsis could narrow racial disparities in overall mortality from severe sepsis (127).

A number of studies investigated the role of markers of infection in ICU practice. The presence of high fever (>39.5°C) was associated with worse clinical outcomes (128). One study found that a protocol based on serial procalcitonin measurements allowed a reduction of antibiotic treatment duration and exposure in patients with severe sepsis and shock without apparent harm (129). Yende and colleagues showed that among patients who survive to hospital discharge after community-acquired pneumonia, many leave the hospital with ongoing subclinical inflammation (as measured by increased interleukin [IL]-6 and IL-10 levels), which is associated with an increased risk of death (130).

Using Bayesian analysis of all trials of antithrombotic therapies (activated protein C, antithrombin III, tissue factor pathway inhibitor) for treating sepsis, Kalil and Sun estimated a substantial probability that activated protein C may be an ineffective treatment for severe sepsis and that a large confirmatory trial is needed (131, 132). A more readily available anticoagulant, unfractionated heparin, was evaluated as a treatment for septic shock in a prospective propensity matched cohort study (133) and was associated with reduced mortality; we await evidence from clinical trials (clinicaltrials.gov identifier NCT00100308).

A retrospective single-center study found that providing early adequate antibiotics and achieving adequate global perfusion, but not liberal vasopressor therapy, were associated with reduced organ failures after septic shock and called for a clinical trial to compare conservative versus liberal vasopressor use in septic shock (134). Granulocyte-colony–stimulating factor did not improve outcomes of patients with septic shock when evaluated in a randomized trial (135).

An interesting study of induced hypercapnia in a sheep model of sepsis found that hypercapnia had similar effects to dobutamine on hemodynamic variables and lactic acidosis. Hypercapnia was associated with improved tissue oxygenation and reduced lung edema formation compared with dobutamine (136). Another study found that plasma concentrations of BNP could be used to identify myocardial depression several days after septic shock (137).

There exist few compelling data to recommend the use of colloids over crystalloids for critically ill patients, yet considering subgroup analyses of the SAFE trial, clinicians wonder whether there may yet be benefits for patients with sepsis. Using data from an international prospective cohort study of patients who were critically ill, the use of colloids or hyperoncotic...
are ongoing (clinicaltrials.gov identifier NCT00133978).

Another area of investigation has been the treatment of systemic inflammation with antioxidants. In a randomized trial of intravenous antioxidants (selenium, vitamin C, vitamin B6, zinc) for patients believed to have oxidative stress (postcardiac surgery, trauma, subarachnoid hemorrhage), there was no effect on organ dysfunction or clinical outcomes (139). Larger studies are ongoing (clinicaltrials.gov identifier NCT00133978).

**SUBSPECIALTY CRITICAL CARE**

**Cardiology, Cardiac Arrest, and Cardiovascular Surgery**

Survival after out-of-hospital cardiac arrest remains poor. A prospective cohort study of ten North American geographic regions found clinically and statistically significant regional differences in out-of-hospital cardiac arrest incidence and outcome (140). Another study suggested that specific hospital-level attributes are associated with improved outcomes after cardiac arrest, including large size, urban location, and teaching status (141). One study validated clinical decision rules for emergency medical services personnel to predict poor hospital outcomes (142); the impact of these rules after inclusion in prehospital resuscitation protocols remains to be evaluated. Persistently low end–tidal carbon dioxide levels during resuscitation may also predict poor outcome (143). A large randomized trial of vasopressin and epinephrine versus epinephrine alone in out-of-hospital cardiac arrest did not change clinical outcomes (144).

The quality of in-hospital cardiac arrest resuscitations may often be poor. U.S. data showed that nearly one-third of inpatients needing defibrillation received it after a delay of greater than 2 minutes; these patients had lower survival (145). Variable hospital staffing may play a role: one study found lower survival rates after in-hospital cardiac arrest during nights and weekends, even in analyses adjusting for potential confounding characteristics. Asystole was more common as the presenting rhythm at night (146).

Given these poor outcomes, improved therapies for cardiac arrest would be welcome. A before and after study showed that a minimally interrupted cardiac resuscitation protocol that prioritized chest compressions for out-of-hospital cardiac arrest improved survival (147). Advanced waveform processing algorithms may permit reliable identification of shockable rhythms by automatic external defibrillators during ongoing chest compressions, decreasing interruptions (148). Another potential prehospital intervention is therapeutic hypothermia during advanced life support, which was described in 33 patients (149).

Sustained arrhythmias are observed in 12% of patients admitted to general ICUs, and ventricular arrhythmias increase the risk of death (150). A systematic review of treatment of new-onset atrial fibrillation in noncardiac ICU patients found only four trials of various drugs for rhythm conversion, highlighting the need define the optimal therapeutic approach to this problem (151). Elevated cardiac troponin values appear to predict postoperative cardiac morbidity and mortality (152), although the pathophysiology and therapeutic implications are unclear.

Several studies addressed the care of patients undergoing cardiac surgery. A large multicenter trial showed a higher risk of death with aprotinin compared with other antifibrinolytics (tranexamic acid and aminocaproic acid) and a similar risk of massive bleeding (153). A large observational study confirmed the increased risk of death in patients given aprotinin compared with aminocaproic acid (154). Another cohort study found that transfusion of red cells stored for more than 2 weeks was associated with a higher risk of postoperative complications and mortality (155). A meta-analysis of 38 randomized trials found that prophylactic desmopressin very modestly reduced transfusion volume (but not the proportion of patients transfused), although the effect was greater in noncardiac surgery (156). Several reports showed that recombinant activated factor VII was effective in controlling coagulopathy in high-risk cardiac surgery, although thromboembolic adverse effects were noted (157). A meta-analysis of 44 randomized trials found that prophylactic corticosteroids for patients placed on cardiopulmonary bypass decreased the risk of postoperative atrial fibrillation and may also decrease bleeding, length of stay, and mortality (158).

Postoperative hypoxemia and atelectasis following cardiac surgery, but not other clinical outcomes, were improved in a randomized trial by a strategy of recruitment maneuvers during mechanical ventilation and noninvasive ventilation postextubation (159). Patients were extubated 4 hours sooner after cardiac surgery using closed-loop adaptive support ventilation compared with pressure-regulated volume-controlled ventilation with auto-mode (160). A novel study found that negative pressure applied to the chest via a cuirass improved cardiac output in patients that were mechanically ventilated after cardiac surgery (161). Intravenous immunoglobulin G did not improve outcomes of patients with severe systemic inflammatory response syndrome after cardiac surgery (162). Observational data suggested that perioperative statins decrease morbidity and death following valve procedures (163) and that preoperative high-dose statins decrease postoperative atrial fibrillation (164). Elevated troponin values appear to predict postoperative cardiac morbidity and mortality in these patients (165).

As surgical techniques change, the need for postoperative intensive care may decrease. A large observational study of abdominal aortic aneurysm repair confirmed findings from randomized trials and found lower short-term rates of death and complications from endovascular compared with open repair, with a longer-term survival advantage among older patients (166). A fascinating 15-patient case series described awake off-pump coronary surgery using thoracic epidural analgesia and femoral nerve block (167).

Sophisticated technologies exist to support patients who are critically ill with cardiac pathology; however, their benefits are still unclear. A study of U.S. Medicare beneficiaries found high early mortality, morbidity, and costs in patients receiving a ventricular assist device, especially when placed after cardiac surgery (168). A small clinical trial showed some physiologic benefits in patients treated with levosimendan, a calcium sensitizer, compared with enoximone, a phosphodiesterase inhibitor, for cardiogenic shock after acute myocardial infarction (169).

The conventional wisdom regarding the role of noninvasive ventilation in cardiogenic pulmonary edema was challenged in a large randomized trial. Gray and colleagues found that noninvasive ventilation and continuous positive airway pressure produced similar faster improvements in respiratory distress and gas exchange compared with standard oxygen therapy but had no effect on short-term mortality (170). The trial faced criticisms regarding exclusion of patients that were sick, lack of adherence to assigned therapy, and overall higher short-term mortality and lower intubation rates compared with previous trials (171).

**Trauma, Other Surgery, Burns, and Poisoning**

A large before and after study questioned the practice of providing advanced prehospital support to patients with trauma, finding no impact on overall survival and worse outcomes in
patients with a Glasgow Coma Score less than nine (172). Complex mechanisms of acute coagulopathy of trauma were elucidated in a prospective cohort study. Hypoperfusion-induced increases in soluble thrombomodulin levels were associated with reduced fibrinogen utilization, reduction in protein C, and an increase in thrombin activatable fibrinolysis inhibitor. Hypoperfusion also resulted in hyperfibrinolysis (173). Blood product utilization, costs, and clinical outcomes in the treatment of massive trauma-related blood loss may be improved by a protocol (174). A systematic review of endovascular stenting for carotid injuries found only 113 patients described in the literature; patency appeared to be high and incident neurological deficits infrequent (175). Bedside echocardiography showed promise in assessing cardiac function in patients with trauma and patients who have undergone general surgery (176).

**Neurologic Intensive Care**

The window for treatment of ischemic stroke with alteplase was successfully extended from 3 to 4.5 hours in a large randomized trial (177). In contrast, promising results from a phase II randomized trial of recombinant activated factor VII for acute intracerebral hemorrhage were not confirmed in a phase III trial, which found slower hematoma growth but no effect on mortality or functional outcomes (178).

Several studies advanced the field of traumatic brain injury. One study found that optic nerve sheath diameter had good correlation with invasively measured intracranial pressure and thus was a promising technique to identify patients with intracranial hypertension (179). A retrospective cohort study found that older adults with traumatic brain injury were less likely to receive a variety of therapeutic interventions and were more likely to die in hospital. Specialist care consultation was associated with a lower risk of death, which may reflect (appropriate) selection bias by referring physicians (180). A small randomized trial suggested that thiopental more effectively controlled refractory intracranial hypertension in traumatic brain injury compared with pentobarbital (181). Another randomized trial investigated an exciting potential new therapy: progesterone increased survival and improved 6-month functional outcomes in patients with severe traumatic brain injury (182). In contrast, a cautionary single-center case series of 40 patients with severe traumatic brain injury treated with decompressive craniectomy found that 70% had unfavorable outcomes (183), underscoring the need for completion of randomized trials (clinicaltrials.gov identifier NCT00155987 and controlled-trials.com identifier ISRCTN66202560).

A nonrandomized crossover study found that a glucose-insulin-potassium infusion improved cardiac function in patients who were brain-dead similar to dobutamine but without tachycardia or hypotension (184).

**Sedation, Analgesia, and Anesthesia**

A randomized trial showed that using the bispectral index (BIS), developed from a processed electroencephalogram in a protocol to guide anesthetic gas administration, did not reduce anesthesia awareness or administration of volatile gases compared with an end-tidal anesthetic gas-guided protocol (185). Another study found that entropy of the frontal electroencephalogram discriminated poorly among clinically assessed sedation states in patients at the ICU, perhaps due to interference from facial muscular activity (186).

The question of whether daily interruption increases benefit when added to a sedation protocol is being examined in a large randomized trial, the pilot results of which confirmed safety and feasibility (187). In weaning patients from mechanical ventilation, melatonin may improve sleep quality and quantity (188).

Airway management is a core ICU skill. Using continuous fluoroscopy, investigators studied cervical spine motion in patients without spinal pathology intubated using manual in-line stabilization after induction of general anesthesia. Compared with direct laryngoscopy, the GlideScope improved glottic visualization but did not decrease cervical spine motion, which was primarily extension in the rostral cervical spine (189). Complications of emergency intubation by residents were significantly reduced (21.7 vs. 6.1%) when attending anesthesiologists were present (190).

**Endocrinology**

The optimal treatment of hyperglycemia during intensive care was again a major focus of research during 2008. Two single-center randomized controlled trials of medical-surgical intensive care patients (523 and 504 patients, respectively) both showed that intensive insulin therapy (glucose 80–110 mg/dl) was not associated with improved survival compared with conventional insulin therapy (glucose 180–200 mg/dl), but led to more hypoglycemia (191, 192). A meta-analysis of 29 randomized trials involving 8,432 patients who were critically ill also concluded that tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia (193).

Several studies examined other aspects of glucose measurement and insulin management. One study raised concerns that under standardized conditions, glucose results from three point-of-care testing devices were inaccurate in ICU patients, and were most frequently falsely elevated, resulting in misinterpretation of high glucose values with subsequent inappropriate insulin administration or masking of true hypoglycemia (194). A retrospective cohort study suggested that increasing glyceremic variability, assessed by the standard deviation of each patient’s mean glucose level, conferred a strong independent risk of mortality (195). Clinician compliance with a computerized glycemc control protocol for patients in the ICU was excellent, and control of blood glucose was better than with a clinical guideline or a paper-based protocol (196).

Two prospective cohort studies of patients who were critically ill and injured surgical patients found that serum estradiol concentrations were higher in nonsurvivors than in survivors (197, 198). The anabolic agent oxandrolone, administered to a cohort of severely burned patients within 7 days of admission and for at least 7 days, was independently associated with higher adjusted survival in a retrospective cohort study of severely burned adults (199). Finally, a meta-analysis of 14 studies including more than 15,000 obese patients found no association between obesity and ICU mortality, but these patients had longer duration of mechanical ventilation and ICU stay (200).

**Hematology**

In critically ill patients with severe renal insufficiency, a single-arm trial found that thromboprophylaxis with dalteparin (5,000 IU once daily) was not associated with an excessive anticoagulant effect due to drug bioaccumulation (as measured by anti-Xa levels) and was unlikely to cause bleeding (201). Similarly, an observational study found an important risk of deep venous thrombosis and major bleeding in ICU patients with severe renal failure, but the risks were related to patient illness severity or other factors unrelated to dalteparin thromboprophylaxis (202).
fusion consistently increased the risks of infection, ARDS, multiple organ failure, and mortality (203). A retrospective single-center cohort study found an increased risk of infection after transfusion of frozen plasma (204). However, a large European multicentre cohort study conducted in the early 2000s found no association between red blood cell transfusion and ICU mortality, which the authors hypothesize may be due to more widespread leukodepletion (205). Similar questions are being studied in critically ill children. One study found that these children are at high risk (74%) of developing anemia and receiving a blood transfusion (49%), which is associated with worse outcomes (206).

Recent studies refute earlier findings of hopeless prognosis when patients with malignancies are admitted to the ICU, which often justified therapeutic nihilism at the bedside. In one study, patients with hematological malignancies required more ICU resources but had similar mortality to other patients when adjusted for illness severity (207). Another study observed a dramatically improved survival of cancer patients with septic shock over approximately the past 10 years (208). A systematic review of 23 studies of pediatric ICU admissions after hematopoietic stem cell transplantation found no relationship between year of study and ICU mortality, which was 60% overall and 71% if mechanical ventilation was required (209). Finally, a large population-based cohort study showed that adult patients admitted to the ICU during a subsequent hospitalization after being discharged after bone marrow transplantation have a poor but not uniformly fatal prognosis, even if they receive invasive ICU procedures (210).

Gastroenterology and Nutrition
The gut is increasingly recognized as an important organ system in the critically ill. A gastrointestinal failure score was developed that incorporated variables of enteral feeding tolerance and intra-abdominal pressure, with worse scores independently associated with increased ICU mortality (211). In a small randomized trial of medical patients with sepsis, early enteral immunonutritive feeds combined with pharmaconutrition (glutamine dipeptides, vitamin C and E, β-carotene, selenium, zinc, and butyrate) caused organ function to recover significantly faster than in control subjects (212).

Renal Physiology and Dysfunction
Definitions of acute kidney injury (AKI) vary. One single-center retrospective cohort study found that the AKI Network’s proposed definition (increment of serum creatinine ≥0.3 mg/dL or ≥50% from baseline within 48 h or urine output <0.5 mL/kg/h for >6h despite fluid resuscitation) predicted hospital mortality, need for renal replacement therapy, and prolonged hospital stay among patients in the medical ICU (213). A large U.K. retrospective cohort study confirmed previous work and found that severe AKI (defined as serum creatinine ≥3.4 mg/dL and/or urea ≥112 mg/dL during the first 24 h) remains common (incidence 6.3%) and highly lethal (hospital mortality 55.8% and 77.3% for nonoliguric and oliguric AKI respectively) (214). A large Australian retrospective cohort study found that AKI secondary to sepsis was common and associated with higher illness severity and risk of mortality compared with non–sepsis-related AKI (215). Even without AKI, ICU-acquired hypotension and hypernatremia are common and are associated with increased risk of hospital mortality (216).

Two systematic reviews synthesized evidence regarding the provision of renal replacement for patients with AKI. One review that included 30 randomized controlled trials and 8 prospective cohort studies concluded that intermittent and continuous modes had similar outcomes, but that higher dose therapy should be provided when continuous modes are used (217). Another review also found no difference between intermittent and continuous renal replacement on survival or renal recovery, but argued that current trials had limited scientific rigor (218). In the context of ongoing uncertainty regarding optimal intensity of renal replacement, Desai and colleagues found that daily (compared with alternate-day) hemodialysis had a favorable cost-effectiveness profile under most scenarios (219). Recent (16) and anticipated (clinicaltrials.gov identifier NCT00221013) results may rapidly alter current recommendations regarding dialysis intensity.

Effective pharmacologic therapy for AKI remains elusive. A small factorial randomized trial of N-acetylcysteine and fenoldopam for patients at high-risk undergoing cardiac surgery found small biochemical improvements in renal function from both interventions in adjusted analyses (220). Another trial found a trend to less AKI in similar high-risk cardiac surgical patients, but no effect on renal replacement therapy or mortality (221). Perioperative human atrial natriuretic peptide infusion for abdominal aortic aneurysm repair showed promising effects on renal biochemistry and urine flow in a small randomized trial (222).

INTERESTING HYPOTHESES
Each year provides new research, albeit preliminary or inconclusive, that suggested a new idea or extends an interesting finding and leaves us anticipating a follow-up investigation. In a small comparison of mechanically ventilated patients who were brain-dead (with no diaphragm activity) and intra-operative patients (with a much shorter period of diaphragm inactivity), diaphragm muscle specimens from patients who were brain-dead showed marked myofibril atrophy. This finding may imply that controlled mechanical ventilation leads to diaphragmatic proteolysis due to inactivity, but the interpretation is confounded by other profound differences between the two patient groups (223).

Invasive fungal infections are a rare but important cause of mortality among patients who are immunosuppressed. The presence of galactomannan, an aspergillus cell-wall component, in bronchoalveolar lavage fluid displayed encouraging operating characteristics in identifying Aspergillus species (224). In children with septic shock, a serum IL-8 level of 220 pg/ml or less, obtained within 24 hours of admission, predicted a high likelihood of survival; this finding may be helpful in clinical practice and clinical trials (225).

Sepsis is characterized by inflammation and coagulopathy and corresponding alterations in vascular reactivity and integrity. Circulating endothelial and platelet-derived microparticles have recently been described in animal models of sepsis and appear to be protective against vascular hyporeactivity and hypotension (226).

Animal studies show efficacy of intravenous lipid emulsion in the treatment of severe cardiotoxicity associated with local anesthetics, clomipramine, and verapamil, possibly by trapping such lipophilic drugs in an expanded plasma lipid compartment. Among several case reports, one described a 17-year-old girl with cardiovascular collapse after bupropion and lamotrigine overdose who was unresponsive to 70 minutes of standard resuscitation but regained an effective and sustained pulse 1 minute after intravenous injection of 100 ml of 20% lipid emulsion (227).

PRACTICAL CLINICAL POINTERS
Some major medical journals now provide web-based videos teaching common procedures relevant to critical care, including catheterization of the subclavian (228) and femoral veins (229), cricothyroidotomy (230), and peripheral intravenous cannulation (231).
An interesting study implemented a real-time method for monitoring pulse pressure variability using standard monitors and found similarly high sensitivity and specificity for the prediction of fluid responsiveness as in previous studies (232). A small study of 71 patients undergoing early tracheostomy after spinal stabilization found a low risk of infection even after the anterior approach (n = 32); no patient required additional surgery (233).

**ICU ORGANIZATION**

**ICU Organization Models and Pay-for-Performance**

Two studies highlighted that the twin effects of an aging population and more prolonged ventilation in many patients will substantially increase the demand for ICU resources in the coming decade (234, 235). One study proposes that the adjusted cost per day in ICUs may be staying relatively constant over time (236).

Quality of care continues to be an important area of research. Adverse events in the ICU are common and independently contribute to death (237). A pharmacist presence in the ICU improves adherence to sedation guidelines and may reduce the duration of ventilation (238). Continuous in-hospital staff intensive care is gaining momentum in North America. One study found that this approach was associated with improved processes of care and staff satisfaction and decreased ICU complications and hospital length of stay (239). In a modeling exercise using previously published data, it was estimated that over 4,000 lives in eight states alone could be saved by transferring patients that require mechanical ventilation to referral centers as opposed to providing care in hospitals infrequently providing ventilation (240). Despite few specific interventions to reduce mortality, there is evidence that overall hospital mortality is falling for patients that are critically ill (241).

**Physician Training and Work Hours**

In a single-center study, increased resident on-call workload was associated with more sleep loss, longer shift duration, and a lower likelihood of participation in educational activities (242). The Institute of Medicine published a report endorsing reduced resident work hours, specifically, maintaining an 80-hour work week maximum and ensuring on-call no more frequently than every third day, 48 hours off after three consecutive nights of duty, 5 days off per month and 1 day per week, and a maximum shift length of 30 hours with 5 hours of interrupted time for sleep between 2200 and 0800 hours (243).

**Palliative and End-of-Life Care**

Providing appropriate and compassionate care at the end of life is an increasing focus of critical care medicine. One French study found a minority of patients had family or loved ones present at the time of death, most had respiratory distress, a significant number were in pain, and only 35% of nurses judged the quality of dying acceptable (244). A U.S. study characterizing the withdrawal of life support process found that for nearly half of patients, the withdrawal process took over 1 day, and that a longer time in the ICU and extubation prior to death were associated with greater family satisfaction (245). An anonymous survey of attending physicians, residents, and nurses at two teaching hospitals found that most physicians believe nurses should be allowed to initiate do-not-resuscitate discussions with families and, according to a small randomized controlled trial of protocol-directed sedation management, physicians believe that medications prescribed to relieve suffering sufficiently hasten death, but are not reluctant to do so (253). Finally, the state of Washington became the second U.S. jurisdiction, after Oregon, to allow physician-assisted death, with the Act taking effect on 4 March 2009 (254).

**ICU Transfers and Outreach**

Rapid response, medical emergency, or outreach teams continued to be both implemented and studied. A single-center U.S. study using interrupted times-series methodology evaluated the effect of a three-member rapid response team, composed of an experienced ICU nurse and a respiratory therapist, on inpatients with evidence of acute physiological decline. They found a nonsignificant reduction in hospital-wide code rates but a significant reduction in outside-ICU code rates and no change in hospital-wide mortality (255). Transition from the ICU to the ward can be stressful for patients and families (256). Simple transfer scores have been developed to predict readmission (257). Despite prior studies to the contrary, nighttime discharge from the ICU was not independently associated with readmission (258).

**KNOWLEDGE TRANSLATION**

**Guidelines**

New publications during 2008 included an update on the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock (259), clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock (260), and recommendations for end-of-life care in the ICU (261). Meanwhile, a systematic review of older professional society critical care guidelines and consensus statements (1990 to May 2007) found that overall quality, as assessed by three published quality instruments, is low but increasing over time (262).

**Implementation of Protocols**

Several trials evaluated the effectiveness of protocols for changing clinician behavior. A cluster randomized trial in 27 intensive care units in Australia and New Zealand showed that a multifaceted-practice change strategy targeting a nutrition support guideline resulted in greater nutritional adequacy and earlier feeding but no improvement in clinical outcomes (12). In contrast, a small randomized controlled trial of protocol-directed sedation man-
agement in an Australian ICU did not reduce mechanical ventilation or length of stay (263). Protocols may also improve the adherence to lung-protective ventilation strategies in patients with ALI. A study in nine Baltimore teaching hospitals observed that only 46% of eligible patients received low tidal volume ventilation (tidal volume \(\leq 6.5\) ml/kg), but the vast majority (81%) of patients were being ventilated with tidal volumes \(\leq 8.5\) ml/kg, and only a very small number (1%) were being ventilated with clearly injurious tidal volumes (\(>11.5\) ml/kg) (264). However, the application of a unit-based written protocol was associated with a sixfold greater odds of receiving tidal volumes \(\leq 6.5\) ml/kg. Finally, an uncontrolled before-after study reported that the implementation of laboratory testing guidelines in a surgical ICU reduced the number of laboratory tests by 37%, with these effects sustained at 1 year (265).

QUALITY

A large observational study using Taiwan’s national health insurance database showed that a higher pneumonia case volume of physicians in the ICU was strongly correlated with lower in-hospital mortality (266), and this relationship persisted when the patients of pulmonologists and intensivists were studied separately. The benefits of having clinical pharmacists in the ICU were explored using information from a 2004 survey of Medicare providers. This revealed that the mortality risk for Medicare patients with nosocomial infections, community-acquired infections, and sepsis in ICUs that did not have clinical pharmacists, was 23.6% higher than those that did have clinical pharmacists (267). A daily rounding checklist improved process of care and patient outcomes in a before and after study in a single-center trauma ICU (268).

Patient Safety

In France, an observational study highlighted the risk of adverse events in critically ill patients. A total of 39% of patients experienced at least one and 23% experienced two or more prespecified adverse events (237). Another study highlighted the limitations of occlusion alarms for peristaltic infusion devices from four manufacturers, especially at low flow rates (269).

A single-center cohort study showed that both arterial catheter colonization and rates of catheter-related bloodstream infection were similar to those in concurrently sited and identically managed central venous catheters, suggesting that arterial catheters should be accorded the same degree of importance as the central venous catheter as a potential sepsis source (270).

ETHICS

Several studies highlighted how underlying cognitive biases can influence treatment decision making. Physicians’ appraisals of underlying disease prognosis were shown to be context-specific, varying depending on whether the physician was randomized to evaluate the patient during an episode of septic shock or during an uneventful clinic visit (271). A simulation study found that physicians from the same institution varied significantly in their decisions about whether to admit to the ICU and on how to manage a hypothetical elderly patient with end-stage cancer (272). Discordance in treatment preferences between physicians and the general public was evaluated in a postal questionnaire sent to random samples of the adult population and of intensivists and neurosurgeons in Sweden. In this study, a majority of physicians stated they would withhold life-sustaining neurosurgical treatment for a hypothetical patient following intracerebral hemorrhage, whereas only a minority of the general public would do so (273).

Research Methodologies and Consent

The challenges of conducting research involving incapacable patients were explored in several studies. An observational multicenter study reported that three-fourths of critically ill patients were unable to provide informed consent throughout their ICU stay, even after extubation, usually due to delirium or sedation. The researchers described a two-step consent process incorporating the Richmond Agitation-Sedation Scale and Confusion Assessment Method for the Intensive Care Unit as a means of rapidly screening critically ill patients before a more detailed traditional assessment of capacity is conducted (274). A survey of attendees at community meetings for an emergency research protocol revealed that although 82% concurred with conducting the study in their community, 30% would not willingly choose to participate in the proposed research (275). A survey of the Canadian Critical Care Trials Group and Australian and New Zealand Intensive Care Society Clinical Trials Group explored the opinions of critical care researchers about enrollment practices, including co-enrollment into multiple trials, consent approaches for incapacable patients, and alternative study designs such as factorial and cluster randomized trials (276).

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