Critical illness is an iatrogenic disorder

John C. Marshall, MD, FRCSC

Iatrogenic illnesses are those that arise as a result of the process of medical care and are potentially preventable by improvements to patient care. The term is commonly used to denote medical error; however, for the critically ill patient the term has a much more fundamental meaning. Critical illness is inherently iatrogenic: it only develops in those patients who have been resuscitated from an otherwise life-threatening disorder, and its subsequent evolution is shaped by the beneficial and adverse consequences of therapeutic and supportive interventions. The construct of organ dysfunction describes both the nature of this support and its inadvertent consequences. This review explores evolving evidence on the iatrogenic nature of critical illness and the implications of an iatrogenic model of disease on the taxonomy, management, and prevention of the complex processes that threaten to limit the survival of the critically ill patient. (Crit Care Med 2010; 38[Suppl.]:S582–S589)

Key Words: iatrogenesis; intensive care; multiple organ dysfunction syndrome; resuscitation; organ system support

The word *iatrogenic* comes from the Greek words for healer or physician (*iatros*) and birth or origin (*genesis*). It denotes illness that is caused not by random forces of nature, but by the direct activities of the doctor. The word is commonly used to denote medical errors or procedural complications (1, 2). Iatrogenic injury, for example, includes a pneumothorax after attempted insertion of a subclavian catheter, or upper gastrointestinal bleeding in a patient receiving heparin.

The concept of iatrogenesis as it encompasses the clinical course of critically ill patients in an intensive care unit (ICU) extends beyond the known risks and inadvertent consequences of intervention. Critical illness itself is an intrinsically iatrogenic state. It only arises in survivors of a life-threatening insult, and its subsequent course is shaped and defined by the same interventions used to sustain life. In the absence of deliberate medical intervention, the course of the acutely ill patient with hypovolemic shock, overwhelming infection, or acute respiratory distress is one of physiologic deterioration and death. In his *Book of Prognostics*, Hippocrates describes the clinical features of impending death: “a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted and their lobes turned out; the skin about the forehead being rough, distended, and parched; the color of the whole face being green, lack, livid or lead-colored . . . it is to be known that certain death is at hand” (3). What to the father of Western medicine was the signature of the end of life is to the contemporary intensivist an indication for fluid resuscitation and a spectrum of active interventions that will transform imminent death into survivable critical illness.

However, after the decision to intervene, the clinical course is shaped by the sequelae of that intervention. Fluid resuscitation in the face of altered capillary permeability restores perfusion, but at the cost of diffuse tissue edema; increased capillary permeability in the lung gives rise to the early features of acute respiratory distress syndrome (ARDS) and leads the clinician to intubate the patient and initiate mechanical ventilation. Sedation is administered to attenuate the associated discomfort, but the inadvertent consequences include hypotension that is treated with vasopressors and apnea, which provokes a decision to institute fully controlled ventilatory support. In concert with the inhibition of upper airway defenses by an endotracheal tube and suppression of the cough reflex by sedation, strategies to prevent stress ulceration or provide enteral access for feeding further promote the risk of acquiring ventilator-associated pneumonia. Tissue edema and vasoactive medications impact regional blood flow and impair renal function. At the same time, cyclic stretch injury by positive pressure ventilation causes further injury to the vulnerable lung, contributing to the worsening of ARDS, whereas antibiotics initiated to combat a suspected infection or a newly diagnosed ventilator-associated pneumonia disrupt normal microbial homeostasis, predisposing to superinfection and the emergence of resistance. The phenotype of critical illness changes rapidly from the specific features of the disease that led to ICU admission to the generic, syndromic abnormalities that are recognized as critical illness. This clinical picture is so familiar that its roots in discrete clinical decisions are readily overlooked.

It is instructive to view the complexities of the state of critical illness through the prism of iatrogenesis—not to scold or to invite structural solutions such as protocolization of care, but rather to explore the more fundamental implications of an inevitable aspect of therapeutic success.

The Multiple Organ Dysfunction Syndrome: A Metaphor for Iatrogenesis

The creation of the first ICUs in the 1950s was a natural consequence of the development of a spectrum of advances in the resuscitation and support of the severely ill or traumatized patient. An improved understanding of the pathologic mechanisms underlying hemorrhagic shock (4) enabled rational approaches to
fluid resuscitation and transfusion and the development of a simple technique to catheterize the subclavian vein (5) that set the stage for techniques that could monitor central hemodynamic function. The polio epidemic in Denmark in 1952 fostered the innovative approach of using a cuffed tracheostomy tube and positive pressure ventilation (delivered by nurse anesthetists, interns, and medical students) and ushered in a new area of support for acute respiratory failure (6). Techniques for hemodialysis developed in the 1940s (7) were adapted for the management of acute renal failure during the Korean War. Thus, in the space of a few years, effective approaches for the support of otherwise lethal organ insufficiency were introduced into medical practice. Soon thereafter the first ICU appeared as a venue where these techniques could be applied to the support of the gravely ill patient (8).

As ICUs became standard fixtures within the healthcare system, a spectrum of new disorders emerged—derangements defined in large part by the availability of interventions to treat them but, more insidiously, having their origins in those same interventions. The entity of ARDS (9), originally described as high-output respiratory failure (10), could only occur because mechanical ventilation averted death from acute respiratory failure, and its clinical description emphasized the disorder as a disease of the lung because it was managed predominantly through ventilatory support. Septic shock, a rare entity before the 1950s (11), came to prominence because techniques of fluid resuscitation and cardiovascular support enabled recovery from overwhelming infection; again, the emphasis on shock and the associated cardiovascular abnormalities reflected the fact that these abnormalities were measured and supported (12). Like the apocryphal story of the blind men trying to describe an elephant, the complex pathologic state of critical illness was described through the lens of the clinical intervention available to monitor and manage it. ARDS, septic shock, acute renal failure, and disseminated intravascular coagulation could coexist in the same patient, but the differential processes of care involved in managing each created the illusion that these were discrete and separate processes.

The concomitant occurrence of life-threatening failure in multiple organ systems was first described in 1969 (13), but it was Arthur Baue who placed these in their contemporary context in an editorial in which he suggested that: “The major limiting factor after injury in patients who do not have brain injury is not so much a system, but rather a combination of events that can best be called multiple systems failure . . . .” (14).

The construct is now called the multiple organ dysfunction syndrome reflects the dynamic interaction between a life-threatening insult, the response of the host, and the capacity of the clinician to provide exogenous support to an organ system that is, often only transiently, incapable of supporting vital function (Fig. 1). The response of the doctor staves off imminent death but, as argued here, fundamentally shapes the subsequent evolution of a clinical state suspended between life and death.

One can describe organ dysfunction from various perspectives—as a clinical syndrome comprising several key abnormalities (for example, ARDS), as a physiologic derangement (for example, hypoxemia despite supplemental oxygen, reflected in a reduced P02/FIO2 ratio), or as the intervention used to manage the deranged state (ventilatory support). In attempting to place the focus on the anticipated harm of clinical intervention, this review discusses the iatrogenic roots of organ dysfunction from the perspective of the intervention.

**Lung Dysfunction: Ventilator-Induced Lung Injury**

The recognition that ARDS was as much a disease of the ventilator as it was a disease of the lung was a direct consequence of the use of computerized tomography. Whereas conventional plain films portray ARDS as diffuse bilateral fluffy infiltrates, the findings on computed tomography scan are much more heterogeneous, being strikingly characterized by consolidation and atelectasis in dependent lung zones, with cystic lesions in the antidependent zones (15) (Fig. 2). Speculation that overdistention of the lung by high peak inspiratory pressures might contribute to the evolution of ARDS (16) prompted clinical trials of lung-protective ventilatory strategies. These revealed that minimizing inspiratory pressures and limiting lung hyperinflation can improve outcomes in ARDS (17–20), even in the absence of concomitant acute lung injury (21).

Lung-protective ventilation strategies also result in attenuation of the release of inflammatory mediators (22), consistent with the concept that lung injury resulting from mechanical ventilation is another important trigger for the complex inflammatory response that underlies the development of the multiple organ dysfunction syndrome (23). Experimental studies reveal that injurious mechanical ventilation strategies not only trigger in-
Engineering mediator release but also result in the apoptosis or programmed cell death of renal epithelial cells in association with impairment of renal function (24).

The mechanisms through which positive pressure ventilation induces lung injury are incompletely understood but are almost certainly multifactorial. Positive pressure ventilation alone activates transcription factors associated with proinflammatory gene expression (25), and mechanical stretch of pulmonary microvascular endothelial cells triggers their release of interleukin-8, a potent chemotactant for neutrophils (26). Lung injury is further exacerbated by overdistention and, presumably, by hypoxia resulting from focal areas of atelectasis (27). Furthermore, rodent studies have shown that ventilation with a large tidal volume induces cholesterol-dependent surfactant dysfunction (28). Hyperoxia (29), altered local antioxidant defenses (30), and even endotoxin in the inhaled gas (31) may further contribute to injury and the activation of a local inflammatory response. Interestingly, ventilator-induced lung injury appears to require intact signaling through toll-like receptor 4 (32), a canonical pattern recognition receptor that not only confers sensitivity to endotoxin but also is activated in response to substances such as oxidized phospholipids (33) and other products that are released after tissue injury (34).

In its earliest phases, the clinical syndrome of ARDS arises from the effects of fluid resuscitation in the setting of altered pulmonary capillary permeability, but successful resuscitation and support introduce an entirely new and entirely iatrogenic element—i.e., injury induced by the effects of the mode of ventilatory support. Recognition that the treatment has become a component of the disease opens the door to supportive strategies that may minimize the inadvertent damage associated with ICU support, strategies such as neurally assisted ventilatory assist (35) or high-frequency oscillation (36). This conceptual model has been best elaborated in understanding the pulmonary derangements of multiple organ dysfunction syndrome but applies to other systems as well.

Cardiovascular Dysfunction: Fluids and Vasoactive Agents

Like the institution of ventilatory support, fluid resuscitation and hemodynamic stabilization are fundamentally important in enabling immediate survival from a variety of life-threatening insults (37, 38). In the same way, hemodynamic resuscitation shapes the subsequent iatrogenic course of critical illness.

Hemorrhage or dehydration impair oxygen delivery to tissues by reducing intravascular fluid volumes. However, the hemodynamic defect in acute illness is usually more complex than a simple deficiency of intravascular volume. Alterations in capillary permeability, in vascular resistance, and in microcirculatory flow create a more complex state for which simple replacement strategies may be insufficient. In some clinical circumstances, the impact is intuitively obvious. For example, aggressive resuscitation of patients with penetrating trauma can worsen clinical outcomes by promoting further uncontrolled bleeding (39); therefore, hypotensive resuscitation may be more appropriate. In other circumstances, the inadvertent consequences of hemodynamic support are less predictable.

Aggressive fluid resuscitation in the face of altered microvascular permeability results in increased extravascular water, and the increased distance across which oxygen must diffuse leads to tissue hypoxia. Tissue edema may be an inevitable consequence of adequate early resuscitation, but there is evidence that fluid restriction reduces the duration of mechanical ventilation and ICU stay in patients with acute lung injury (40). The benefits of conventional resuscitation protocols are dependent on the timing of their implementation, with benefit evident early during the course of hemodynamic instability (37, 41), although not when the protocol is instituted later during the ICU course (42). How the selection of resuscitative fluid might result in differential benefit or harm is still controversial and likely varies with the nature of the underlying insult. Overall, in a heterogeneous population of ICU patients, there was no obvious benefit for albumin over saline as the resuscitative fluid (43). Within this heterogeneous group of patients, however, albumin appears to benefit patients whose underlying diagnosis is sepsis, but it appears to harm those with traumatic brain injury (44). Furthermore, certain synthetic colloids are associated with an elevated risk of renal dysfunction (45).

Vasoactive agents are commonly administered with the intent of increasing tissue oxygen delivery, but the biological plausibility is far from established and the clinical benefits are unproven. Studies in patients with septic shock show that increasing mean arterial pressure with vasopressors often increases cardiac output and has no effect on oxygen delivery, lactate levels, or renal function (46, 47). Rather, the net consequences of elevating blood pressure by increasing peripheral resistance may be reduced tissue blood flow and clinical harm. Zakrison et al (48), for example, found that, independent of the blood pressure target, patients...
who received vasopressor agents after intestinal reconstruction had a higher rate of anastomotic leaks. A randomized trial of L-NMMA, a potent vasopressor by virtue of its ability to inhibit inducible nitric oxide synthase, showed that targeting increased blood pressure in septic shock resulted in increased mortality (49). Other strategies to increase oxygen delivery, including the use of inotropes agents (50) and blood transfusion (51), have also been associated with net clinical harm. Vasopressor use has been identified as an independent risk factor for the development of deep venous thrombosis in critically ill patients (52).

The fact that harm has been demonstrated in a number of studies of resuscitation in critical illness in no way challenges the fundamental concept of resuscitation: however, it does argue for more sophisticated and nuanced strategies. For example, mean arterial pressure is commonly used as both a diagnostic marker of inadequate tissue perfusion and a target for resuscitation. However, pressure is being measured as a surrogate for flow and, given the mathematical relationship between pressure, resistance, and flow, a comparable flow can be achieved at a lower pressure when resistance is reduced as it is in sepsis.

Renal Dysfunction: Toxins and Altered Splanchnic Flow

Acute kidney injury is a complication of renal ischemia and of exposure to a variety of nephrotoxic agents, including medications and radiocontrast materials (53). Other specific etiological factors are less well-characterized, although a body of evidence suggests that renal failure results from the apoptotic death of renal epithelial cells (54), and experimental data show that renal epithelial apoptosis can be induced by injurious mechanical ventilation (24).

Aggressive fluid resuscitation can also induce inadvertent renal failure. Increased interstitial edema with a resulting loss of compliance of the abdominal wall is an important contributing factor to the abdominal compartment syndrome; the consequent elevation in intra-abdominal pressures, by impeding venous return from the kidney, can reduce renal perfusion pressure (55).

Neurologic Dysfunction: Sedatives, Analgesics, and Paralytics

Sedative and analgesic agents are the most commonly used medications in the ICU; their use alleviates pain and anxiety but is also implicated in preventable iatrogenic complications of critical illness. Individual agents have well-recognized adverse consequences, for example, bradycardia and acidosis as elements of the propofol infusion syndrome (56), adrenal insufficiency as a consequence of etomidate (57), and delirium as a result of benzodiazepine use (58).

Beyond these specific effects, oversedation poses the additional iatrogenic risks of prolonged dependency on ICU supportive care and its associated morbidity (59). Liberation from mechanical ventilation is delayed and has the attendant risk of ventilator-induced lung injury, and the cough reflex is suppressed, predisposing to microaspiration and ventilator-associated pneumonia. Independent of the agents used, sedation strategies that deliberately seek to expedite weaning are associated with improved clinical outcomes (60).

Immunologic Dysfunction: Disruption of Normal Host Microbial Homeostasis

Disruptions in normal host microbial homeostasis are among the most profound but least understood iatrogenic alterations in critical illness. In health, the human body is colonized by a complex indigenous microbial flora that is in intimate association with mucosal surfaces. Bacteria of the indigenous flora outnumber host cells by a factor of 10 to 1 (61), comprise in excess of 1000 distinct microbial species (62), and exert potent influences on normal development and function.

Critical illness is associated with profound alterations in the composition, invasiveness, and virulence of the indigenous gut flora. Alterations in colonization patterns of the proximal gut, an area that is normally sterile, are particularly prominent. The colonizing species are the same organisms that are responsible for nosocomial ICU-acquired infection (63, 64), and abnormal colonization is associated with a greater severity of organ dysfunction and an elevated mortality risk (Fig. 3). At the same time, the

![Graph A](image1)

![Graph B](image2)

**Figure 3.** Proximal gut overgrowth in critical illness. Quantitative cultures from the stomach, duodenum, and proximal jejunum of a cohort of critically ill patients reveal significant overgrowth with the same flora that predominate in intensive care unit (ICU)-acquired infections, and patients with such colonization have more severe organ dysfunction than those colonized with other species \( (*p < .05) \). (A) The ICU mortality rate for patients colonized with either *Pseudomonas* or *Enterococcus* was significantly higher than that for patients not so colonized (black bars, colonized patients; clear bars, patients who were not colonized with the particular organism; \( *p < .05 \)). Data from Marshall et al (64). *Staphylococcus epidermidis*; *S. epidermidis*, *Staphylococcus epidermidis*; *S. fecalis*, *Staphylococcus fecalis*.
diversity of the fecal flora is reduced (65). Observational data suggest that alterations in the composition of the proximal gut flora can result in invasive infection either through the aspiration of colonized gut secretions or through the process of bacterial translocation across an intact gut mucosa. Further evidence for a truly pathogenic role of altered gut flora in critical illness derives from studies of selective digestive tract decontamination; systematic review of the results of approximately 50 trials reveals that inhibition of proximal gut colonization with aerobic Gram-negative organisms and fungi can reduce the risk of nosocomial infection, the severity of organ dysfunction, and, ultimately, the risk of mortality (66).

Iatrogenic factors that may predispose to altered gut colonization and increased rates of bacterial translocation include the use of antacids, H2 antagonists, and proton pump inhibitors, lack of enteral feeding, and the use of broad-spectrum antimicrobial agents. Sedation and the supine position predispose to microaspiration (67).

There is also experimental evidence that altered gut colonization can induce systemic changes in immunologic and metabolic homeostasis. Gut colonization with Gram-negative bacteria (68) and portal venous, but not systemic, infusion of killed Gram-negative bacteria (69) induce manifestations of immune suppression characteristic of critical illness. Portal endotoxemia also induces evidence of a systemic hypermetabolic state (70), whereas parenteral nutrition results in an amplified systemic response to endotoxin challenge in healthy volunteers (71).

Other Iatrogenic Determinants of the State of Critical Illness

Multiple other potentially lifesaving interventions can contribute to the development of organ dysfunction in the critically ill patient, and to the phenotype of critical illness. A comprehensive catalog is beyond the scope of this review, but several merit special mention.

Blood transfusion has been independently associated with increased organ dysfunction in critically ill patients (51, 72). Transfusion is a potent stimulus for inflammatory gene expression after trauma (73, 74). The administration of fresh-frozen plasma has also been linked to ARDS and an increased risk of organ dysfunction (75). Total parenteral nutrition has been associated with liver dysfunction in the critically ill patient (76), as well as with an increased risk of nosocomial infection (77). Finally, even religiosity and variability in the approach to end-of-life care can modify the phenotype of illness in the ICU by sustaining or limiting interventions such as ventilation or feeding (78).

Iatrogenesis in the ICU: Implications for Research and Clinical Care

Characterization of critical illness as an iatrogenic process is not simply sophistry, i.e., a clever but ultimately trivial way of thinking about a complex process. Some elements of iatrogenesis are readily recognized and easily modifiable. Process changes can minimize or eliminate errors associated with the administration of medications (79). The development of checklists and management bundles can reduce the morbidity associated with procedures such as central line insertion (80) or the management of more complex disorders such as sepsis (81). However, the implications of an iatrogenic model of critical illness are much more fundamental. Recognition that the very nature of critical illness is the end-product of deliberate clinical decisions suggests the need for nuanced changes in approaches to description, management, and prevention that might minimize harm and improve clinical outcomes.

Iatrogenesis and the taxonomy of critical illness

Whereas critically ill patients vary widely in the spectrum of illnesses that lead to their admission to an ICU, their clinical phenotypes and the spectrum of possible interventions that arise after admission are much more constrained. Whether the admitting illness was necrotizing pancreatitis, multiple trauma, variceal bleeding, endocarditis, or thrombotic thrombocytopenic purpura, the spectrum of interventions directed at the underlying cause is limited, and the focus on ICU decision-making lies on the basis of an arbitrary level of hypoxemia, a nonspecific pattern of changes on the chest radiograph, and some assurance that these are not a consequence of cardiac failure (82). The predisposing clinical setting is diverse, and the pathologic processes responsible for the clinical phenotype vary over time. Enhanced pulmonary capillary permeability and neutrophil influx predominate in the early phases, whereas the sequelae of added ventilator-mediated injury and fibrosis and tissue repair shape the later stages. A definition that focuses on the consequences for the lung and that fails to encompass the differential pathologic processes evolving over time also fails to adequately stratify patients who might benefit from interventions to alter the early permeability changes in some cases or prevent the later sequelae in other cases.

Equally, a failure to differentiate a pathologic state from the clinical decision that is made to treat that state risks conflating disease and clinical decision-making; therefore, it potentially obscures modifiable behaviors that can alter the course of illness. It is common, for example, to speak of the “need” for mechanical ventilation or vasopressor support, although the benefits of intervention are established and unassailable. Decisions about ventilatory support or the use of vasoactive medication are clinical decisions based on a limited evidentiary knowledge base, whose benefits for the patient are not known. Convention dictates that in patients with severe sepsis and septic shock, we should increase the mean arterial pressure to 65 mm Hg with the use of vasopressors (83), but this is a matter of clinical habit, not intrinsic patient need, and it remains unproven what is the optimal blood pressure to maximize survival and whether the level is the same in all patients. And when we measure organ dysfunction using the level of...
treatment as the measure of severity, as occurs, for example, when vasopressor use is the measure of cardiovascular dysfunction (84, 85), we may confuse intrinsic patient severity with suboptimal and modifiable clinical practice.

Iatrogenesis and the management of the critically ill patient

If iatrogenic factors are an important determinant in the course of critical illness, then it follows that minimizing iatrogenic injury is a key objective of clinical care. In the simplest formulation, iatrogenic injury can be reduced by minimizing exposure to ICU interventions by minimizing sedation, by liberating the patient from ICU support, and by discharging the patient from the ICU as expeditiously as possible. It can be argued that the primary goal of ICU care is to get the patient out of the ICU and in as brief a time as possible, ideally alive, but if survival is overwhelmingly improbable then with a death that is dignified and consistent with patient and family wishes as possible (86).

Just as there is no intrinsic need for specific ICU interventions, so there is no compelling reason to target normalcy in supporting the critically ill patient. Ample evidence in multiple differing domains suggests that normal values may be suboptimal in the critically ill patient. Thus, targeting more normal levels of hemoglobin (51), glucose (87), or carbon dioxide and tidal volume (19) are all associated with worse clinical outcomes. A priority for ICU clinical research is to define the difference between normal and optimal physiology in the critically ill patient.

Prophylaxis of iatrogenic morbidity in the critically ill patient

Perhaps the most important implication of viewing critical illness through the prism of iatrogenic complications is that these are potentially preventable; defining optimal prophylactic strategies is a clear priority for clinical research. The prevention of iatrogenic complications implies that the primary focus on ICU-based research might be the minimization of harm, rather than the optimization of benefit—a subtle but important shift in research approach. The scope of such an approach is broad. How do we balance patient comfort against the adverse effects of sedation, optimize the benefits of antibiotics while minimizing such consequences as superinfection and resistance, or support the circulation while minimizing the contrasting harms of vasoconstriction and fluid overload? Metrics that better reflect the evolution of new iatrogenic change after ICU admission are central to detecting harm, and organ dysfunction scores—calculated as new-onset organ dysfunction over time or delta scores (88)—hold the promise of serving this role, although the methodology of such scores is still underdeveloped (89).

A research focus on minimizing harm associated with the spectrum of ICU interventions, rather than on introducing and evaluating novel technologies, will have minimal traction with the pharmaceutical or device industries, and so these investigations will go to investigator-led clinical trials groups. More than a dozen such groups are active around the planet and have recently come together in a collaborative research effort to understand the epidemiology and optimal management of severe H1N1 infection (90). Given the substantial costs and morbidity associated with critical illness, it will be incumbent on peer-reviewed funding agencies and other public bodies to ensure that funding is available for the rigorous evaluation of evolving critical care practice.

CONCLUSIONS

The construct of disease carries an inherent sense of fatalism and inevitability. A disease can be understood as a process of deranged physiology or function, often having an identifiable cause (and so being amenable to preventive measures) but clearly representing a pathologic state that is distinct from that of other diseases. Critical illness and its syndromic manifestations—ARDS, sepsis, and organ dysfunction—are not inevitable but deliberate; they are not so much diseases as consequences of increasingly aggressive medical and surgical interventions. Their prevention or management requires an understanding of the elements of medical commission that shape their emergence.

REFERENCES

20. Meade MO, Cook DJ, Guyatt GH, et al: Ventilation strategy using low tidal volumes, re-

Crit Care Med 2010 Vol. 38, No. 10 (Suppl.)


Copyright (c) Society of Critical Care Medicine and Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.


