Critical care "normality": Individualized versus protocolized care

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Patients with critical illness are heterogeneous, with differing physiologic requirements over time. Goal-directed therapy in the emergency room demonstrates that protocolized care could result in improved outcomes. Subsequent studies have confirmed benefit with such a "bundle-based approach" in the emergency room and in preoperative and postoperative scenarios. However, this cannot be necessarily extrapolated to the medium-term and long-term care pathway of the critically ill patient. It is likely that the development of mitochondrial dysfunction could result in goal-directed types of approaches being detrimental. Equally, arterial pressure aims are likely to be considerably different as the patient's physiology moves toward "hibernation." The agents we utilize as sedative and pressor agents have considerable effects on immune function and the inflammatory profile, and should be considered as part of the total clinical picture. The role of gut failure in driving inflammation is considerable, and the drive to feed enterally, regardless of aspirate volume, may be detrimental in those with degrees of ileus, which is often a difficult diagnosis in the critically ill. The pathogenesis of liver dysfunction may be, at least in part, related to venous engorgement that will contribute toward portal hypertension and gut edema. This, in association with loss of the hepatosplanchnic buffer response, it is likely to contribute to venous pooling in the abdominal cavity, impaired venous return, and decreased central blood volumes. Therapies such as those used in "small-for-size syndrome" may have a role in the chronic stages of septic vascular failure. (Crit Care Med 2010; 38[Suppl.]:S590–S599)

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Critical illness, regardless of its etiology, is a highly abnormal state in physiologic and physical terms. Our role as intensivists should be to provide a safe and supportive environment in which an individual patient's homeostatic processes can return to health. There continues to be a tendency to assume that normalizing measured numbers and physiologic parameters will facilitate this process of recovery. Certainly, it makes the charts look "better." However, the hard evidence for improved or faster recovery by undertaking such treatments is lacking. One of the issues pertaining to examining the literature is the manner in which research is undertaken and presented. The nature of a randomized controlled trial is to have a given hypothesis and to then choose a patient cohort with strict eligibility criteria. Many of the patients we, as clinicians, see coming through our care are often excluded. Furthermore, standards of care with the area of interest of the trial product often are not addressed. So, how should we treat patients who would have been excluded from such trials? More often than not, it seems that the desire to undertake something new and exciting wins and patients are offered the "new, better management." The phenomenon of "product/protocol" creep is observed and outcomes of diverse groups then are not investigated effectively. Case series equally have a tendency to report only positive findings, and thus their suggested treatments should also be viewed with a degree of suspicion. Another potential issue is that the patient cohort in the critical care environment is far from homogeneous. Even within a variety of subgroups there is marked variability in the severity of organ failure, physiologic derangement, and precipitating factors. Furthermore, the disease, or at least its phenotype, changes. Thus, the optimal treatment regimen for an individual in the first 48 hrs of an acute insult is likely to differ greatly from that at 7, 14, and 21 days into a period of critical illness. Should a secondary episode of nosocomial sepsis in the critical care environment be treated in the same manner as in someone who has been on a general ward for the previous week or weeks, or as in someone presenting *de novo* to the emergency room? Antibiotic selection will obviously need to vary, depending on the situation. Maybe other treatment protocols and hemodynamic aims to obtain optimal outcomes should vary, also. Can it be appropriate to suggest that a patient who presents with a fever, tachycardia, and mean arterial pressure of 60 mm Hg with a normal urine output and creatinine be treated in an identical manner as someone with a similar picture who is already 2 wks into critical care and in established renal failure? We have learned the lessons with respect to mechanical ventilation and that striving for normal levels of $Paco_2$ is potentially detrimental. Yet for a variety of other support methods and interventions, we remain addicted to making the charts and organ functions look "normal." Are we treating our patients or ourselves?

Standards of Care and Protocols

At present, a main driver of quality and consistency in critical care practice, and medicine as a whole, is the development and subsequent application of standards of care, checklists, protocols, and integrated care pathways. Having parameters is useful in providing consistency of delivered care, especially in the initial stages of sepsis or acute illness, or in a patient undergoing a specific, clearly defined procedure. They allow staff, the pa-

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tient, and their loved ones to be able to track an expected clinical course. They are, by definition, most applicable to a patient whose clinical course is within the "normal range" and who has a limited number of comorbidities (1). However, some patients are outside the defined group for which the pathway was designed. In these scenarios, a proscribed care pathway may result in mediocrity or impaired outcomes for that individual vs. the benefit achieved for the majority. A standard care pathway/protocol is ideal for many yet should not be viewed as "tablets of stone." Instead, one should be able to say, "this applies to most patients but is it suitable in this particular setting, and if not, why not?" Let us encourage thought because surely this is how we innovate. Thinking outside the "black box" of "normal" should be encouraged and form as much a part of ongoing education as the ability to review and cite guidelines.

We should recognize that guidance is frequently developed from controlled trials that excluded patient groups and, also, may fail to be replicated in the future. Furthermore, in assessing guidelines, one should be aware of the evidence that resulted in their development and to consider that composition of multiple strands of guidance may or may not result in a sum benefit.

Treatment protocols should also attempt to recognize the presenting phenotype. We no longer try to make the patient suit the ventilator, having developed more elegance and understanding in this area. However, for managing inflammation and organ dysfunction, we still seem to insist that the patient has read and conforms to the textbooks! It is likely that an individual's presenting phenotype, determined no doubt by a mixture of environment, genetic profile, and microRNA (2, 3), should result in a variety of possible treatment options. We recognize the detrimental effects of activation of the sympathetic nervous system in many organ systems and the potential detriment of tachycardia in respect to endothelial function (4). Similarly, in the critically ill individual, the role of adrenergic stress may be modulated by the individual phenotype or, in some situations, agents that modulate these effects may prove beneficial (5, 6). Recognition of individual response parameters should result in individualized as opposed to generic care. So, for some, beta-blockade or corticosteroids or epinephrine may provide benefit. In another context, a pressor without alpha or beta activity, such as vasopressin, may be optimal. Recognition of these differences may enable improved outcomes and permit greater understanding of the observed variance in outcomes after similar insults. The development of point-of-care biomarkers to individualize care should be an achievable aspiration of critical care.

Another aspect of protocolized care and guidance that requires comment is the manner in which they are subsequently applied as assessment tools of the quality of delivered care. Health care systems are, quite appropriately, striving to optimize quality and cost-effectiveness. In health management terms, guidelines provide an ideal format with which to score clinical services; a guideline exists and, as such, percentage compliance with said guidance can be presented as a quality measure. It is essential that clinicians are actively involved in the design of the audit tools, allowing divergence and innovation to be applied in appropriate clinical scenarios without the hospital management presenting an intensive care unit as providing poor standards of care based on compliance with guidance alone. Similarly, we must ensure that our energies are not focused on gaming audit results but in educating clinicians in the physiologic building blocks of critical care and ensuring they are provided with appropriate analytical and applied skills. To illustrate these points, I review different systems and highlight a few examples of what I believe to be inadequacies and discrepancies in our current thought processes and management regimens.

Cardiovascular

Blood pressure, fluid balance, cardiac index, and, increasingly it seems, the central venous oxygen saturation are frequently at the forefront of daily management plans within the intensive care unit. The clarity of thought I used to have as a junior staff member with regard to these parameters has declined in parallel with years of practice and amassed experience.

The evidence for striving for a given blood pressure is fraught with difficulty. What is "normal"? Is "normal" that which an individual would have when healthy and walking around in the upright position or while asleep? Should we temper our target to that which is "acceptable" in the first 48 hrs of sepsis/acute insult vs. that needed for a later state of established organ "failure/hibernation" or "incipient organ dysfunction/hibernation"? Again, the clinical context and course for the individual patient is paramount in this decision paradigm. The pendulum of expert opinion swings widely from pressure or flow being the optimal end point of resuscitation. However, rarely, if ever, do we define the exact points of clinical care being examined, even though most studies relate to *de novo* admissions as opposed to the "long stayer." We must not lose sight of the optimal end point, namely, recovery/regeneration of organ function. Ironically, in the long-term patient this requires us to maintain particular attention to detail. It may be that the aims and objectives over a given time course are variable and disparate.

A target mean arterial pressure (MAP) may be achieved with judicious intravenous fluid administration and, thereafter, with various vasoactive agents. The evidence base for a given blood pressure for physiologic functionality has not been determined; many would aim for an initial MAP of 70 mm Hg, with increased levels being striven for in the context of cerebral insults and attempts to preserve renal function. However, the data are far from clear. Within the neurologic literature there is the concept of the Lund hypothesis (7, 8), whereas in acute liver failure lack of autoregulation to pressure frequently results in MAP and intracranial pressure increasing in parallel (9, 10).

Recent case series provide some insight, albeit in general terms, with regard to MAP and eventual outcome. In a cohort of 111 cases of septic shock, logistic regression analysis for 30-day mortality showed MAP and lactate on arrival were significantly associated with 30-day mortality (10). Receiver-operator curves were plotted and the highest area under the curve value (0.835) was found for MAP $<$65 mm Hg, suggesting this cut-off may be optimal. Many reviews and guidelines for the management of septic shock target values of MAP between 60 and 75 mm Hg. The rationale to keep pressures higher than 60 to 65 mm Hg is that this is the level for many organs in which autoregulation ceases and flow becomes pressure-dependent. However, one of the risks of setting a given blood pressure as a sole end point of therapy is the tendency to increase pressure in the face of an under-resuscitated circulation, leading to excessive constriction, poor end-organ perfusion, and impaired microcir-

culatory flow (11–13). Dubin et al (12) showed decreased capillary perfusion density with increasing MAP, albeit with considerable individual variation. The optimization of flow and pressure in the management paradigm remains uncomfortable as the assessment of optimal fluid loading before the institution of pressors and inotropes remains generally inadequate. Use of pressure measures alone are likely to result in some receiving fluid who are already fluid-replete, whereas others will receive vasoconstrictor agents who would benefit from further volume (14). Equally, it must be recognized that dynamic measures of volume responsiveness, such as stroke volume variation and pulse pressure variation, are not applicable in the setting of cardiac arrhythmias and significant respiratory efforts.

Dunser et al (15) also examined arterial blood pressure during early sepsis and the relationship with eventual outcome. Interestingly, the area under the receiver-operator curve for 28-day mortality was greatest for values of MAP <60 mm Hg and mean perfusion pressure (measured as MAP central venous pressure) <45 mm Hg. A MAP value <60 mm Hg increased the risk of death by 2.96 (95% confidence interval, 1.06–10.36), whereas the need for renal replacement therapy was best predicted by MAP values <75 mm Hg. Notably, in many studies and in clinical practice, even if the MAP target is set at 65 mm Hg, there is a tendency for "pressure creep," with increasing doses being administered to drive the MAP higher. A fundamental question that needs to be addressed as we examine the psychology of the workplace, and particularly that of the critical care area, are the bedside drivers of resident and nursing staff in the end points they achieve as opposed to those suggested.

Care should ideally be tailored to an individual's needs. This was demonstrated in the renal bed by Deruddre et al (16), who showed that renal blood flow, as assessed by renal Doppler studies, was highly variable in response to changes in MAP achieved by infusion of norepinephrine. Optimal flow was achieved at varying blood pressure for different individuals. Bourgoin et al (17) similarly showed no benefit with regard to renal function when MAP was increased from 65 to 85 mm Hg. Of interest, in the neonatal intensive care literature, the concept of permissive hypotension is considered in those with signs of good perfusion. Outcomes were similar to those with normotension, whereas worse outcomes were seen in those in whom hypotension was treated (18).

The aforementioned studies relate to the initial stages of management of sepsis and septic shock. It may be that at this stage the clinical scenario is that of jeopardized organ function as opposed to failure/hibernation (19, 20). Thus, the parameters one may wish to strive for in conditions of acute reversibility will differ from those required a few days later when there is, for example, established renal failure. Driving pressure through a renal vascular bed when the kidney has been oligoanuric for >48 hrs is unlikely to result in normalization of function. Would a management protocol addressing such parameters result in speedier recovery of function? There is a lack of appropriate trials addressing this. Given the concern that inappropriate vasoconstriction may be detrimental, MAP values of 60 to 65 mm Hg may be adequate if there is adequate perfusion and end-organ function is stable. It has been suggested that continuous renal replacement therapy may favor renal recovery over intermittent continuous renal replacement therapy. However, studies by Palevsky and Vinsonneou (21–23) suggest that 60-day outcome is the same. In both studies the incidence of hypotension was 30% to 39% (defined as systolic blood pressure <80 mm Hg), yet renal recovery was seen in >90% of patients regardless of the mode of continuous renal replacement therapy applied. This may suggest that hypotension, although not persistent, does not impair renal recovery and that the assumed safer mode (continuous renal replacement therapy) in fact had as many complications as, if not more than, intermittent continuous renal replacement therapy. Another compounding issue associated with many of the forms of continuous renal replacement therapy in patients with sepsis is the lack of definitive data regarding appropriate dosing of antibiotics and antifungals, especially in the context of high volumes of distribution (24, 25).

Determination of adequate perfusion (both at whole body and organ levels) is problematic as the patient progresses from insult and precarious organ function to established organ dysfunction/hibernation. Several groups utilizing *in vitro* microscopy have elegantly examined the microcirculation (particularly sublingual) and observed pathologic responses to certain constrictor therapies (26). Regarding whether these findings relate to endothelium activation and inflammation, the effects of constrictor therapy or to altered flow based on changing cellular requirements in the face of mitochondrial dysfunction is yet to be elucidated, as is the relationship to outcome.

It is also difficult to accurately predict how microcirculatory flow and oxygenation respond to vasoconstrictors and dilators (11, 27). For example, no difference in microcirculatory flow parameters was seen with or without nitroglycerine when a strict resuscitation protocol was utilized (28). Importantly, pressors are likely to have different effects on different organ beds; for example, the gut may be particularly sensitive to vasoconstrictor agents (29, 30). "Aggressive" control of blood pressure with constrictors after appropriate fluid loading may be optimal in the short-term but could prove detrimental over the medium term and longer term in a manner similar to what we now recognize for fluids. A fine balance exists between too much and too little. Perhaps we should utilize more sophisticated techniques, e.g., assessing tissue oxygen content and microcirculatory flow (26), although we should not lose sight of old-fashioned clinical skills such as detecting "warm edges" on the patient.

The type of vasoactive agent should also be considered. Vasopressin, norepinephrine, and epinephrine are, at present, the most commonly administered pressor agents. However, other approaches should not be discounted, even nitric oxide synthase blockade. Perusal of the major clinical trial investigating nitric oxide synthase blockade in septic shock suggests that, maybe, the "baby was thrown out with the bath water" (31), because many of the negative effects could have been the result of overzealous vasoconstriction. The data on vasopressin use are also unclear with regard to outcome benefit, although it would seem a useful adjunct to improve responsiveness to pressor agents, providing excessive doses are not administered (32–34). The risks of overconstriction and end-organ hypoperfusion holds with every agent, but perhaps especially in those with isolated pressor activity.

The finding of a relationship between mean perfusion pressure and 28-day outcome (15) is physiologically intuitive given that organ perfusion is determined

by the pressure gradient across any given organ. However, it is rare in modern intensive care unit practice to consider this variable except in the context of abdominal hypertension and abdominal compartment syndrome, in which intra-abdominal pressure may be considered a vital factor affecting renal and gut perfusion (35). Perhaps these physiologic relationships, in association with central venous pressure, should be evaluated in more detail to consider transmural pressure gradients. The finding of an elevated central venous pressure and a low perfusing pressure (mean or, more importantly, diastolic pressure) will significantly impact on coronary perfusion and, hence, cardiac performance. Especially in the face of a tachycardia and/or pulmonary hypertension and right heart dysfunction, this can result in inadequate substrate delivery to the cardiomyocyte. Early work by Cunion et al (20) showed equivalent coronary blood flow but no myocardial lactate production in those with and without cardiac dysfunction, raising the possibility of loss of autoregulation, disordered microcirculatory flow, and/or mitochondrial dysfunction. Investigators have demonstrated increased coronary sinus blood flow, particularly in those who failed to survive, with evidence of decreased stroke volume and ejection fraction despite elevated cardiac indices. Substrate utilization was altered with decreased fatty acid utilization and increased lactate consumption (36–38). We see little evidence of overt myocardial ischemia in the critically ill patient; however, elevated troponin levels are not uncommon. This could be, perhaps, viewed as a biomarker of myocyte stress, particularly in the early phases of sepsis and initial therapy, marking patients at higher risk for mortality, albeit acknowledging that renal clearance is a confounder (39–41).

Measuring and correcting central venous saturation ($ScvO_2$) now features strongly in sepsis guidelines (42, 43). The finding of a low value certainly warrants investigation and may be multifactorial; alterations in hemoglobin, oxygenation, and cardiac output should be considered, as should potential artifacts such as an erroneous catheter tip position. Equally, the finding of an elevated $ScvO_2$ should not be taken as explicit that the patient is volume-replete, especially in the setting of hyperdynamic states and microcirculatory failure. A recent study (44) examining initial management of sepsis in the emergency department used protocols that included a central venous pressure >8 mm Hg; however, reported levels were between 11 and 16 mm Hg at 0, 24, 48, and 72 hrs after study entry.

Immune Status

The immune effects of the agents we administer equally should not be ignored (45–47). Epinephrine, as an example, has significant effects on leukocyte mobilization and demargination (48), whereas catecholamines in general induce an inflammatory response in hepatocytes (49). This may be physiologically beneficial in the early stages of sepsis, facilitating protection from invading pathogens; however, in the later stages of disease progression, they may be highly detrimental. Persistent stimulation with catecholamines (exogenous and/or endogenous) and circulating cytokines may contribute to transformation of monocytes to an endotoxin-tolerant, anti-inflammatory phenotype that may have implications in patients requiring prolonged critical care (50–52). Neutrophil function is also abnormal with disparity between opsonization and respiratory burst, and this also varies over time (53–56). Other agents commonly used in the critically ill also have significant effects on immune function. Etomidate is known to decrease adrenal function, whereas agents such as ketamine may be potentially beneficial through modulating the nitric oxide, carbon monoxide, and hydrogen oxide pathways (57–59). After endotoxin administration to rats, ketamine resulted in hepatic protection mediated, at least in part, through heme oxygenase-1 and carbon monoxide (59).

The clinical tendency to date has been an attempt to manipulate patients toward immunologic normality, with early dampening followed, potentially, by subsequent stimulation. Is either of these endeavors appropriate? If the hypothesis of "hibernation" is a clinical reality at certain time points during the clinical course, then being in a state of relative anergy could even be beneficial. Thus, immunostimulatory interventions may potentially prove detrimental. Many of our trial interventions in sepsis have been excessive and have also failed to impact positively on outcomes, e.g., (60, 61). In alcoholic hepatitis, the use of a tumor necrosis factor monoclonal antibody in combination with steroids resulted in increased mortality, even though studies using tumor necrosis factor monoclonal antibody alone did not show harm (62, 63). Equally, in the animal literature, stimulatory agents such as granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor did not inevitably result in improved outcomes, albeit in patients there are some data suggesting decreased duration of mechanical ventilation and intensive care unit stay (64–66).

Finally, we should recognize that our decisions are based on levels of circulating cells and not those causing effects at sites of inflammation. This may be highly pertinent because some of the so-called states of functional immunoparesis we encounter may actually represent an effect of inflammation and resolution of inflammation at the primary site. As such, peripheral stimulation of immune functionality may have the potential to worsen organ function and delay healing (67, 68).

Renal, Intra-Abdominal Pressure, and Fluids

Perfusion pressure within the abdominal cavity may impact significantly on organ function. For example, pressure in the renal vein is similar to that in the abdominal cavity. Work in patients with cirrhosis has shown that, in the presence of ascites, renal vein pressure is frequently ≥20 mm Hg (69). However, drainage of large volumes of ascites has been associated with increased markers of renal dysfunction and sympathetic nervous system activation. The rationale probably relates to the marked reduction in intra-abdominal pressure being associated initially with improved venous return and cardiovascular stability, followed, over time, by splanchnic vasodilation, venous pooling, and, hence, volume depletion (70). These effects can be countered with appropriate volume loading or maintaining a given intra-abdominal pressure, possibly by administering a splanchnic vasoconstrictor. Similar physiologic changes are also likely to be seen in a critically ill patient. This may be of particular concern given that fluid therapy may be detrimental in intra-abdominal hypertension, hence propagating the tendency to overconstrict to achieve a given MAP or abdominal perfusion pressure. That high intra-abdominal pressure (>25–30 mm Hg) is detrimental is clearly established (71–74). There is, however, less clarity regarding the opti-

mal management of increased pressures below these levels. Ascitic drainage easily can be undertaken under ultrasound guidance and ileus diminished with nasogastric drainage. Whether decompressive laparostomy is appropriate in the context of a nonsurgical abdomen is considerably less clear. In those in whom laparostomy is undertaken, consideration should be given to the fluid and nitrogen losses that can occur (75).

Renal outcome has been examined with regard to MAP in several studies. Again, optimal renal perfusion pressure has yet to be established, but it is unlikely that therapeutic manipulations will have an effect on anything other than the acute stages of the renal insult. So, at what time point is it acceptable to drive the target mean arterial pressure to, for example, 75 mm Hg? Perhaps only for the first 48 hrs of presentation or oliguria would seem logical. Oliguria seems to prompt clinicians to reach for fluids and pressor agents, but it should perhaps be viewed with a degree of equanimity. Initially, it should be viewed as a "red flag" to ensure there is no reversible cause. If the oliguria persists, then instead of pouring in fluids—of dubious quality and effect—or potentially excessively vasoconstricting with pressor agents, oliguria could be viewed as an appropriate physiologic response to an insult. The desire to generate urine, regardless of quality, is then normally addressed through the liberal administration of diuretics. Even in those relatively rare cases in which a response is seen, the quality is usually poor and the metabolic side effects, which are significant, are largely ignored. A major failing is the tendency to provide inadequate hydration with crystalloid solutions while avoiding the detrimental effects of hyperchloremia (76). The excessive administration of colloid has rightly received poor press, with several studies showing that both starch and gelatin solutions are associated with increased rates of acute renal injury (77–79), and that a positive fluid balance is associated with increased mortality (80, 81). However, the large, blinded, multicenter study of Finfer et al (82) showed overall no difference between groups randomized to crystalloid or 4.5% human albumin solution. Nevertheless, subgroup analysis did suggest a potential benefit of albumin in the sepsis group but harm in patients after trauma, particularly head injury. Hepatology studies (83–86) attest to the beneficial effects of albumin, albeit 20% solutions, in both bacterial peritonitis and hepatorenal failure. However, the SOAP study found that albumin therapy was associated with increased mortality (87). Perhaps the role of albumin should be addressed as a potential drug rather than as a simple fluid. It is an antioxidant and a binder of various vasoactive substances (88, 89); the hemodynamic benefits observed during molecular adsorbents recirculation system treatment may, at least in part, be attributable to "cleansing " of native circulating albumin and thus improving its binding capacity (90). Importantly, all commercial albumin solutions contain preservatives. A study examining stimulation of peripheral monocytes in the presence of albumin solutions with and without the presence of preservatives suggests that, at least *in vitro*, the preservative-treated albumin has anti-inflammatory properties (91). Thus, in the setting of an acute systemic inflammatory response and a hyperactive immune response, it could be postulated that infused albumin may act as both a volume expander and an anti-inflammatory agent and have potential benefit. By contrast, infusion of albumin later in the clinical course when the immune status is anti-inflammatory may be detrimental to outcome.

Goal-Directed Therapy, Lactate, and Glucose

The role of protocolized care may be suitable for the initial stages of sepsis (43, 92); however, its benefits may be more dubious and potentially even detrimental in patients with established organ dysfunction. The original work of Rivers et al (93) has been repeated in different contexts and does appear to be beneficial in the emergency department setting (94). Contextually, this is logical and similar to the "golden hour" of trauma, i.e., early flow-driven resuscitation is beneficial. In many aspects the care pathway is similar to that of the preoperative and perioperative surgical patient at high risk in whom optimization of fluid status and flow improved outcomes with decreased morbidity and shortened length of stay (95–98).

It should be noted that the care bundles and protocols recommended for managing sepsis utilize many of the support systems that are now being questioned, such as steroids for vasopressor dependence (99). By contrast, protocolized optimization of the patient with established critical illness (addressing oxygen delivery, uptake, and cardiac indices) has failed to improve outcome and may actually increase mortality (100). Caution thus should be addressed in extrapolating data from one clearly defined clinical context to the whole management process of the critically ill patient with established organ failure/dysfunction. Targets of $ScvO_2$ and central venous pressure are contentious end points for resuscitation in this context. Venous pressure needs to be addressed as a dynamic response variable with intra-abdominal pressure taken into account. $ScvO_2$ is likely to be influenced by the high-output states that are often the standard in established organ failure. In this case, a high $ScvO_2$ may not be reflective of adequate volume status but more a reflection of cellular dysfunction and limited oxygen uptake—cytopathic dysoxia. Studies demonstrate that high and low $ScvO_2$ levels are associated with poor outcome (101). Recent work has also suggested that lactate is a powerful prognosticator in patients with sepsis independent of organ failure and shock (102). Clarity in regard to what is optimal remains elusive, so one of the great potential benefits for adopting protocols, at least in the short term to medium term, may be attention to detail with improved outcomes in a manner similar to that observed when enrolled into a clinical trial.

The elevated $ScvO_2$ seen in many patients with organ failure and critical illness may be driven by the hyperdynamic state with shunting through the microcirculation and/or cellular dysoxia. Previously, a high $ScvO_2$ and low oxygen extraction ratio were thought to represent inadequate nutritive flow. The assumption that increasing oxygen uptake would result in improved outcome resulted in a series of studies driving cardiac output with pressors and inotropes; such studies resulted in increased mortality (100) or no benefit (103). Elevated lactate levels were also thought to be the result of tissue hypoxia, although various studies have now demonstrated that this is largely a result of aerobic glycolysis and increased Na^+/K^+ATPase activity in skeletal muscle (104–106) with normal tissue oxygen levels. This should not suggest that lactate is not a useful biomarker; it remains a strong prognostic marker and represents a balance between cellular production driven by aerobic glycolysis and the capacity of organs, particularly the liver, to metabolize the available lac-

tate. It is frequently responsive to fluid loading, at least at initial presentation. The finding of normal tissue oxygen levels has resulted in the suggestion that much of the organ dysfunction in critical illness is related to mitochondrial dysfunction, although not all the literature supports this view (20, 107–109). Mitochondrial function is reported in various articles to be unchanged or decreased, with decreased activity being seen more frequently in established sepsis (110). Furthermore, this dysfunction is reversible and offers the opportunity for novel therapeutic intervention (108, 111–113).

Tight blood glucose control has been shown in some studies to be either beneficial or harmful, especially in relation to hypoglycemia (77, 114–116). Of interest, however, were the findings from the initial study of Van de Berghe et al (117) that postmortem liver biopsy results of those receiving tight blood glucose control showed significantly less mitochondrial ultrastructural damage and disruption with preserved mitochondrial respiratory chain complex I. These conflicting data should not prevent clinical care striving for reasonable levels of glucose while avoiding low levels.

Liver and Gastrointestinal Function

Liver dysfunction in sepsis is multifactorial in nature (118) but is most prevalent in Gram-negative and intra-abdominal sepsis (119, 120). It is also more likely to be seen in those with abnormal underlying liver function. The observed hyperbilrubinemia is the most easily recognized marker of liver dysfunction, but this does not normally present until some days after the initial insult. Any intervention designed solely to decrease bilirubin is, however, unlikely to be fruitful; bilirubin is a marker of dysfunction rather than an etiological factor.

The splanchnic bed is a large vascular bed with a potentially significant role to play in the cardiovascular and gut failure of sepsis/inflammation. After initial vasodilatation and central volume depletion, there is activation of the sympathetic and renin-angiotensin-aldosterone systems. The vascular supply to the liver is from the hepatic artery and portal vein. Blood flows through a sinusoidal bed, passing down an oxygen gradient from zone one to three. Venous drainage is *via* the hepatic veins directly into the inferior vena cava and back to the right atrium. Thus, elevated right atrial pressures are likely to result in liver congestion and may also elevate portal pressures. Resistance then increases in the organs draining into the portal venous system—the intestine, stomach, and spleen. Significant increases in right atrial pressure will also result in exuduative interstitial edema, with a potential cycle of impaired hepatic venular flow, endothelial inflammation, increased intrahepatic resistance, and, in the longer-term, fibrosis. As portal pressure increases, bowel edema will develop; as portal pressure increases to >12 mm Hg, there is the potential for varices to develop with portosystemic shunting. This allows delivery of endotoxin and bacterial toxins from the gut to enter the systemic circulation with further inflammation and increased risk of further liver involvement.

One of the vascular hypotheses of liver injury promoted by Wanless (121–123) is aligned with the observation of parenchymal extinction and collapse associated with hepatic venous outflow occlusion and is potentially equally applicable to the liver injury seen in sepsis and inflammation. It may be that some of the hyperbilirubinemia observed in the sepsis literature pertains to aberrant vascular flow and parenchymal obliteration in addition to the recognized and more greatly studied changes in hepatocyte transporters and bile flow (124). Animal studies support these hypotheses (125–127). End points of resuscitation should consider the relationship between right atrial and portal pressure; dynamic assessment of liver function should be considered as a potentially important end point. The liver is, especially in this milieu, a highly metabolically active organ, being an intrinsic part of the fixed reticulo-endothelial system and contributing to cytokine production, acute phase response, and drug metabolism, among others. As such, appropriate delivery of both nutritive flow and adequate venous drainage should be viewed as an essential component of management of the critically ill patient. Thus, thoracic but not lumbar epidural anesthesia results in increased indocyanine green clearance after major abdominal surgery (128). Increased intrahepatic resistance plus an increased splanchnic inflow have the potential to result in a pattern of disease similar to that seen after liver resection and living related transplantation, i.e., small-for-size syndrome (129–131). This model may offer alternative treatments for hepatic dysfunction of sepsis, ensuring that portal inflow does not become excessive as liver resistance increases, and considering modulatory agents such as beta-blockers, vasopressin/terlipressin, and other agents that decrease intrahepatic resistance.

The balance between intestinal ischemia and avoidance of splanchnic hyperemia is likely a fine balance. The monitoring tools available at the present time do not readily address these issues. One could perhaps reconsider the use of tonometry when an increase in gastric end-tidal (or gastric arterial) CO_2 gap was classically considered representative of intestinal ischemia, and when those patients whose gap was either normal or resolved with resuscitation were found to have improved outcome (30, 132). One could hypothesize that an elevated CO_2 gap may be representative of impaired venous return, as could be seen in portal hypertension and increased liver resistance. Tonometry in patients recovering from acute liver failure was initially normal and then deteriorated during their period of recovery in a time frame that was associated with the development of portal hypertension (133).

Is it appropriate to insist on early enteral nutrition in all patients in the critically ill environment? Again, a one-size-fits-all checklist approach is likely to benefit perhaps the majority but risks significant detriment to a minority. Certainly, data on early postoperative nutrition appear beneficial. Delivery of food to the gastrointestinal tract will result in increased blood flow to the intestine via the superior mesenteric artery (134). In health, splanchnic flow will remain constant by virtue of the hepatic buffer response; however, in sepsis, this response is impaired (135), with the potential to result in splanchnic pooling and central volume depletion. This, in turn, will result in increased venous drainage through the portal vein and, in a situation of elevated pressures or increased intrahepatic resistance, there will be further venous engorgement with development of spontaneous porto-mesenteric shunts and mucosal edema. In patients with large nasogastric aspirates, gastric emptying is promoted with prokinetics (none of which are without potential side effects), and when it fails a nasojejunal tube may be inserted. In some patients food continues to be delivered to an immobile, poorly functioning gut, and this may result in ileus with periods of sepsis and inflammation from the dilated,

edematous intestine. Normal functioning of a gastrointestinal tract is an excellent prognostic sign, but the extrapolation of forcing the gut to work to achieve an improved outcome is not clear and may be detrimental. In experimental models of superior mesenteric venous ligation, gut edema *per se* has been shown to benefit from feeding (136). However, this may not be replicated in clinical scenarios with the compounding effects of liver resistance and systemic inflammation. People do not wish to imbibe food in large volumes when they have a fever or are otherwise unwell. Although starvation is not an option in the long term, it is likely that early and aggressive enteral nutrition is potentially harmful in some patients, and certainly in those in receipt of high-dose vasopressors (137). A recent study (138) examining enteral feeding with or without probiotics in severe necrotizing pancreatitis and the findings of ischemic bowel should be viewed with concern. It may not so much be the effects of the probiotics that were being observed in this scenario but the effects of enteral feeding in unstable patients with organ failure (139). The effect of enteral feeding on intestinal function also may be related to the timing of feeding in respect to the subsequent insult. Importantly, total parenteral nutrition (TPN), instituted before ischemia, resulted in worsened vascular permeability in distant organs compared with enteral feeding (140). By contrast, involuntary feeding instituted after ischemia reperfusion injury showed worse outcomes (141). Thus, in the context of shock and severe ischemia reperfusion injury, early feeding may be best avoided, at least in the early stages of treatment.

The poor reputation of parenteral feeding dates back many years and is classically associated with villous atrophy, cholestasis, and sepsis. Recent studies from Spain showed that early institution of artificial nutrition appeared protective. However, in multivariate analysis, TPN, sepsis, and excessive calculated energy requirements were risk factors for liver dysfunction (142, 143). It may be that in those with an early liver insult, not yet associated with measured derangement in liver biochemistry, there would be an increase in transhepatic resistance with decreased sinusoidal flow secondary to white cell adherence and sinusoidal endothelial constriction, and subsequent elevation of portal pressure. This cohort will likely demonstrate early intolerance of enteral nutrition and early TPN should be considered. The causal relationship between liver dysfunction and TPN is not clear. The finding of liver dysfunction in the enterally fed group was still significant at 18%, but it was lower than the 30% incidence observed in those who received TPN. Perhaps the latter group had a higher incidence of gut failure and, in some cases, this may have been attributable to early liver dysfunction as delineated. The splanchnic bed remains, in clinical terms at least, something of a "black box." Predictors of gut failure are lacking and indocyanine green clearance has only been taken-up by a small number of enthusiasts. The reluctance to institute TPN should be reassessed and potentially addressed sooner in those who show signs of gastrointestinal intolerance. The risks of TPN-associated liver dysfunction can be significantly decreased by avoidance of overfeeding, appropriate carbohydrate-to-fat ratio, attention to blood glucose control, and scrupulous line care.

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