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SIRS, MODS, and the Brave New World of ICU Acronyms: Have They Helped Us?

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Physicians like acronyms. Whether they denote a biologic entity such as TNF, a physiologic measurement such as CVP, a classification system such as APACHE, a syndrome such as AIDS, a disease such as TB, a therapy such as a CABG or ECMO, or even an investigative undertaking such as GUSTO, there is something both familiar and authoritative about distilling a complex biomedical concept into a short, manageable, and pronounceable group of initials. Acronyms both clarify and obfuscate, and serve to transform an amorphous clinical problem into one or more recognizable conditions for which the possibilities and limitations are recognized. The patient with acute respiratory failure and a diffuse infiltrate on the chest radiograph is an example: Measure the PCWP—if it is elevated it is CHF, otherwise it is ARDS. The clinical shorthand suggests a rapid diagnostic approach and a simple binary approach to management.

Simplification and classification are necessary preconditions for treatment, and the very essence of diagnosis and clinical decision-making Algorithms, whether implicit or explicit, form the foundation of medical practice. However, in the most complex group of patients encountered in contemporary medical practice—the multiply-traumatized or acutely ill patients who are admitted to an intensive care unit (ICU)—the acronyms have proven to be a particularly inadequate embodiment of clinical reality. SIRS (systemic inflammatory response syndrome), MODS (multiple organ dysfunction syndrome), CARS (compensatory antiinflammatory response syndrome), MARS (mixed antagonistic response syndrome), and ARDS, though reflections of evolving concepts of the nature of critical illness, have proven to have limited utility in identifying groups of critically ill patients who might benefit from a particular approach to therapy. Their limitations point to the need for improved understanding of the process of being critically ill.

Concepts, Syndromes, and Diseases of Critical Illness

A ***disease*** is a discrete alteration in physiologic function that brings harm to the host. It may have one or many causes. Cancer, for example, is the disease that results when the normal mechanisms limiting cell growth are perturbed, with the result that such growth occurs excessively and autonomously. Meningitis is a disease that arises because of microbial invasion into the cerebrospinal fluid, its life-threatening manifestations reflecting both the local proliferation of microorganisms and the response of the host to their presence. Whereas a disease is defined by derangement of normal function, its treatments are directed at distinct components of that process. When a cancer is localized, it can be treated by surgical resection. If not, cytotoxic therapy given to inhibit the process of pathologic cell growth may be appropriate. However, it is empirically evident that not all cytotoxic agents work equally well for all kinds of cancer and that not all patients with cancer benefit from a particular therapy.

Thus the development of effective treatment requires two more refinements. The disease must be further classified on the basis of biologic variables to delineate more homogeneous subgroups of patients who may respond to a particular therapy (patients with squamous cell carcinoma of the lung versus those with small-cell lung cancer, for example), and it must be staged so treatment is given to those who are most likely to benefit (patients with high grade carotid stenosis versus those with low grade lesions, for example). Within any given group of patients with a disease process that is relatively homogeneous from a biologic perspective, some have disease that is sufficiently early or sufficiently mild that survival following therapy is virtually certain, whereas others have a process that is so advanced therapy cannot be expected to produce a meaningful response.

A ***syndrome*** is a combination of clinical or biochemical abnormalities thought to be the manifestations of a disease, even when the biologic basis for that disease remains unknown. Prior to identification of the human immunodeficiency virus (HIV), a new syndrome was recognized that was characterized by lymphadenopathy, weight loss, opportunistic infection, and Kaposi's sarcoma; it occurred with increased frequency in certain populations (homosexual men, hemophiliacs, and intravenous drug users).[1] Delineation of this distinctive syndrome aided the search for its cause by focusing attention on a specific group of patients.

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Designation of a combination of findings as a syndrome is an arbitrary process: No formal guidelines exist for a particular combination of abnormalities to be denoted as a syndrome. Rather, the acceptance of a new syndrome reflects its perceived utility by a population of practitioners who can use the criteria to categorize patients to understand their illness or to guide their management. One could, for example, define a lung cancer syndrome characterized by cough, weight loss, hemoptysis, and chest radiographic abnormalities. This notion is unlikely to be attractive to clinicians for two reasons. First, not all patients with lung cancer manifest the syndrome; and conversely, not all patients with the syndrome have lung cancer (they might have, for example, tuberculosis, congestive heart failure, or Goodpasture syndrome). Second, and even more importantly, readily available diagnostic tests such as bronchoscopy with biopsy, mediastinoscopy, and computed tomographic (CT) scanning permit the diagnosis to be made with greater sensitivity and specificity than are afforded by the relatively nonspecific clinical criteria of the syndrome. Thus the terminology "syndrome" is useful when it identifies specific groups of patients who might benefit from specific investigations or therapy, or for whom more specific diagnoses cannot be made readily.

There are, however, a large number of disorders whose pathophysiology is unknown or, if it is understood, has not given rise to effective therapy, and whose clinical boundaries are ill-defined. Some are benign, self-limited conditions. The diagnosis of gastroenteritis, for example, encompasses a large number of disease processes, from viral infections to food hypersensitivity to stress-related disorders; the impetus to provide a more precise diagnosis is small, as the consequences are minor and the symptoms generally of short duration. For other diagnoses the consequences may be more severe, yet the lack of an objective basis for differentiating discrete diseases renders the process of diagnosis uncertain and even controversial. In the past, the diagnosis of consumption gave way to the more precise disease diagnoses of tuberculosis or carcinoma of the lung; and that of chronic intestinal stasis[2] was dismissed as a nonentity. Which of these two paths lies in the future of such current conundrums as environmental hypersensitivity or fibromyalgia is unknown.

For still other disorders, the lack of precise understanding that might define a disease stands as a significant impediment to progress in defining more effective therapies. It is ironic that in the ICU, where more physiologic information is available than in any other venue in the health care system, such challenges are particularly common. Entities such as sepsis, acute lung injury, multiple organ failure, and persistent failure to wean are common and readily recognized by all practitioners. Yet the criteria used to delineate these processes are variable; and for any given patient there is less than perfect agreement among clinicians on whether the process, so readily conceptualized in the abstract, is actually present.[3] It is hardly surprising, therefore, that specific therapies are not available, and that attempts to develop therapies have proven so frustrating.

The promulgation of concepts such as that of SIRS or MODS[4] has perhaps served to bring into focus some key aspects of the nature of contemporary critical illness. Whether these acronyms benefit either the patient or the physician is controversial.[5] This chapter argues that they represent initial steps along the complicated road from compelling concepts, to diseases that can be treated, to improve clinical outcome.

Sepsis, SIRS, and the Inflammatory Response in Critical Illness

The word *sepsis* was first used by Hippocrates more than two millennia ago to denote a process of tissue breakdown that resulted in disease, a foul smell, and death. Sepsis was the negative counterpart to *pepsis*, a process of tissue breakdown that was life-giving and embodied in the digestion of food or the fermentation of grapes to produce wine.[6] With the identification of microorganisms as the cause of infectious diseases, the word sepsis was seconded as a synonym for severe microbial infection, and septicemia denoted the presence of bacteria in the circulation.

Prior to the development of effective antimicrobial therapy, the equation of bacterial infection with the clinical response it evoked was a logical step. The introduction of effective antimicrobial therapy exposed a weakness in this assumption, however, as antibiotics did not eliminate the problem of sepsis but merely changed its epidemiology. Studies of the bacteriology of infections in hospitalized patients showed that the introduction of antimicrobial agents was associated with a shift from a predominance of infections with exogenous species to one of infection with endogenous species, with no significant alteration in the prevalence of such infections in hospitalized patients.[7] With the widespread introduction of ICUs during the decade of the 1960s, there was a further shift in the microbial spectrum. Whereas infections with gram-negative organisms had previously been uncommon, these infections emerged as the most common and certainly the most serious infections faced by critically ill patients.[8] The ability to support vital organ function during an acute infection that would otherwise be rapidly lethal also brought an awareness that the physiologic consequences of infection—the acute changes in hemodynamic, respiratory, renal, and gastrointestinal function—represented an unsolved challenge when managing the septic patient.[9] This conceptual shift marked the beginning of studies that focused on trying to improve outcome by modulating the host response.[10,11]

Two large multicenter clinical trials conducted during the early 1980s tested the hypothesis that survival of sepsis could be improved by the concomitant administration of supraphysiologic doses of glucocorticoids.[12,13] Neither of these studies showed benefit for the experimental intervention, but they ushered in a new era in sepsis research by articulating a series of criteria that purported to identify the population of patients most likely to benefit from immunomodulatory therapy: patients manifesting a series of physiologic abnormalities denoted as sepsis syndrome. *Sepsis syndrome* was defined as the occurrence of tachycardia, tachypnea, hyper- or hypothermia, and evidence of altered organ perfusion in a patient suspected of harboring an infection.[14] The rationale for proposing such a syndrome was

compelling. Preclinical studies suggested that corticosteroids were most effective when given prior to or as soon as possible after the infectious insult. The results of microbiologic cultures are only slowly obtained, and it was therefore desirable to define a set of clinical parameters, present early in the course of the septic process, that would identify patients who were likely to be infected.

The specific features that define sepsis syndrome were established not through an intensive study of the natural history and clinical epidemiology of critically ill patients with life-threatening infection but, rather, through an ad hoc process of consensus, achieved apparently under somewhat testy circumstances in a hotel room in Las Vegas. It is questionable whether the resulting criteria define a syndrome let alone delineate an appropriate population for a clinical trial of high dose glucocorticoids. Tachycardia and tachypnea are highly nonspecific physiologic responses, and temperature changes may or may not be present in patients with infection; establishment of the presence of infection relies on clinical suspicion, a subjective and poorly reproducible variable. Epidemiologic studies of patients meeting these criteria confirm that the patients comprise a highly heterogeneous group with respect to clinical outcome [14] and the presence of the putative mediators of sepsis.[15] Microbiologically proven infection is present in fewer than half of patients with sepsis syndrome. Sepsis syndrome has been used as the entry criterion for most studies of novel approaches to modulate the inflammatory response.[16] The disappointing outcomes of these studies are well known and reflect, in part, the inadequacy of the entry criterion. In fact, recent work suggests that glucocorticoids can have a beneficial effect on outcome when used in a differently defined population: patients with refractory septic shock, defined as prolonged vasopressor dependence.[17]

Dissatisfaction with the terminology used to describe the process of overwhelming inflammation in the critically ill and, in particular, variability in the use of the word sepsis led to a consensus conference jointly sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM). That conference suggested that the word sepsis be reserved for those circumstances in which clinical inflammation arises from invasive infection. It defined infection as a microbiologic phenomenon characterized by the invasion of normally sterile host tissues by microorganisms or their products; it suggested that new terminology was needed to describe the process of systemic inflammation, independent of its cause. Thus the acronym SIRS was introduced into the medical lexicon (Fig. 2.1). SIRS describes the occurrence of the physiologic manifestations of systemic inflammation independent of the cause; sterile causes of SIRS include ischemia, tissue injury, sterile inflammation, drug reactions, and autoimmune disorders.[4]

It has been documented in a number of cohort studies that the inflammatory response, independent of the infections that commonly trigger it, is an important determinant of outcome,[18–20] and the concept of SIRS reflects this evolving understanding. SIRS is an attractive concept, but is it a

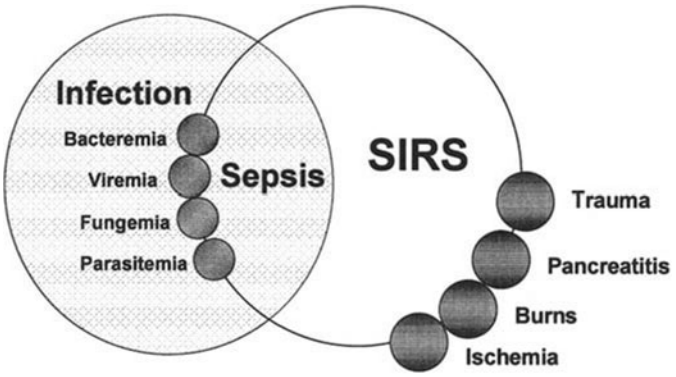

FIGURE 2.1. Interrelation of infection and the host inflammatory response. Infection is a microbial phenomenon characterized by the invasion of normally sterile tissues by microorganisms or their products. Occasionally, those organisms can be isolated from the systemic circulation, giving rise to bacteremia if the organism is a bacterium. The prototypical clinical response that arises in the host in response to serious infection is denoted as the systemic inflammatory response syndrome (SIRS). SIRS is a nonspecific response that is also elicited by trauma, burns, pancreatitis, ischemia/reperfusion injury, drug reactions, and autoimmune disorders. When SIRS arises as a consequence of invasive infection, the process is termed ***sepsis***. (Adapted from Bone et al.[4] with permission.)

syndrome? Using the definition proposed above—a combination of clinical or biochemical abnormalities that indicate the presence of disease—it clearly is not: Although SIRS may develop following administration of a bolus of endotoxin to a human volunteer,[21] it may also develop following or during exercise, stress, or lovemaking. The specific criteria used to defined SIRS are similar to those for sepsis syndrome; and like the criteria for sepsis syndrome, they represent an arbitrary constellation of physiologic abnormalities, rather than an empirically derived set of abnormalities that are known to correlate with the pathologic process of interest. Indeed the basis for selecting the four SIRS variables—tachycardia, tachypnea, hyper- or hypothermia, and leukopenia or leukocytosis—is unclear; consideration of specific criteria for SIRS was not part of the ACCP/SCCM consensus conference. The four SIRS criteria are all components of the APACHE II system, suggesting that they are simply generic severity of illness measures, not specific markers of an exaggerated inflammatory response.

The attempt to define a clinical syndrome or a set of diagnostic variables that reflect the systemic activation of a host inflammatory response stems from a well established concept: Infection and other acute insults such as trauma or ischemia produce tissue injury in the host by inducing the release of injurious mediator molecules from host immune cells, and these mediators in turn are responsible for the physiologic and biochemical alterations seen in the clinical setting. However, the definition of a syndrome requires that it first be shown that the elements of the syndrome reliably reflect the presence of the pathologic process underlying it. Because the mediator response is not well defined in biochemical terms, and because the criteria for sepsis syndrome

or SIRS lack both sensitivity and specificity for establishing the presence of any discrete component of that response, neither can truly be considered to define a syndrome.

Indeed the concept that the inflammatory response defines a syndrome may be inappropriate. Inflammation is less a pathologic process than an appropriate adaptive response to an acute threat to homeostasis; failure to mount that response can also have adverse consequences for the host.[22] The better conceptual model for systemic inflammation may be that exemplified by either the endocrine or coagulation systems: an adaptive process regulating homeostasis that becomes pathologic when it is deficient or overactive. For both processes, the clinical challenge is to characterize the biochemical abnormality using signs and symptoms to trigger investigations. Easy bruising or inappropriate clotting prompt the physician to define a discrete disorder (e.g., deficiency of factor VIII or protein S). Similarly, tachycardia and heat intolerance, two relatively nonspecific symptoms, prompt the physician to evaluate thyroid hormone levels. In both cases specific therapy is directed toward the abnormality in the level of the factor of interest, and in neither is it a prerequisite that we define either a bleeding syndrome or a syndrome of hyperthyroidism. Yet clinical studies of mediator-targeted therapy have proceeded from precisely the opposite direction: study candidates are selected on the basis of meeting nonspecific criteria for sepsis syndrome or SIRS, and levels of the mediator target of interest are not considered when defining the appropriate population to treat. A retrospective analysis of patients enrolled in a trial of an antiendotoxin therapy[23] showed that evidence of benefit was greatest for those patients in whom levels of endotoxin were highest.

Other systems have been developed to describe or quantify the systemic inflammatory response,[18,24] but none has been shown to correlate with a discrete pathologic process that can be modulated therapeutically. It has also been proposed that the complexities of systemic inflammation can be better described through the adoption of additional acronyms: CARS (compensatory antiinflammatory response syndrome) and MARS (mixed antagonistic response syndrome).[25] Although it is certainly true at a cellular level that the activation of proinflammatory mediator synthesis is accompanied by the synthesis of a number of antiinflammatory and regulatory mediators, there is no evidence at the level of the whole organism that this process occurs separately from activation of a systemic inflammatory response (and therefore merits consideration as an entity distinct from SIRS) or, even if it did, that it can be detected by a panel of parameters, either clinical or biochemical, that would justify its being considered a syndrome.

In summary, then, articulation of the concept of SIRS has served to crystallize an evolving biologic concept: that the morbidity of inflammation arises through the response of the host rather than as a consequence of the particular process that triggered that response. SIRS is a constellation of symptoms, rather than a diagnosis, and should trigger a search for the cause of that symptom complex. The reflex administration of antimicrobial agents to patients with signs and symptoms of inflammation will hopefully become less common as the distinction between infecting and the response to infection becomes appreciated by clinicians. On the other hand, precisely because it is a symptom complex rather than a disease, SIRS does not identify any discrete pathologic process that could reasonably be expected to respond to a given therapy. Until we identify the specific diseases for which SIRS is the clinical manifestation, attempts to modulate the host response will continue to prove frustrating.[26]

Organ Dysfunction, Organ Failure, and the Clinical Sequelae of Inflammation

The evolution of concepts of altered organ function in critical illness mirrors the evolution of ideas regarding sepsis and the inflammatory response. The first ICU was established just over 40 years ago as a locale that could provide specialized, life-sustaining organ system support during a period of otherwise lethal physiologic instability.[27] ICUs became feasible because of the development of techniques of organ system support, including positive-pressure mechanical ventilation, renal dialysis, hemodynamic monitoring with support using fluids and vasoactive agents, and parenteral nutritional support. These advances, all arising within the space of two decades, made possible the prolonged survival of a group of patients who during an earlier era would have died a rapid death. They also established a paradigm for providing such support, by focusing on the particular failing systems whose functions were being supported. Organ system insufficiency requiring support was not only an indication for ICU admission but a complication of the clinical course following that admission.

The first descriptive reports of organ system insufficiency in the ICU focused on isolated organ systems such as the lung [28,29] and viewed the derangements of other systems as a manifestation of failure of a single system, for example, ARDS or disseminated intravascular coagulation (DIC). Skillman et al. were the first to suggest that combinations of failing organ systems might represent a distinct problem in critical care.[30] It remained for Baue in 1975 to articulate the notion that the unsolved problem of critical illness was less the failure of a single organ system than the concomitant failure of multiple organ systems and to emphasize how similar the postmortem findings were in a group of ICU patients dying as a result of highly diverse antecedent conditions.[31] This editorial set the stage for a series of descriptive studies of a phenomenon variously known as multiple organ failure,[32] remote organ failure,[33] and multiple system organ failure,[34] which established three important concepts. First, the syndrome was remarkably similar in its expression, even though its causes were highly diverse. Second, the prognosis for patients manifesting this process was a function of the *number* of failing organ systems. Finally, multiple organ failure commonly arose in the wake of a life-threatening infection and on occasion was the first clinical sign of untreated infection.[33,35]

Subsequent studies showed that the prognosis for patients with organ system failure was a function not only of the number of failing systems but also of the severity of dysfunction within

each system.[36,37] Thus the ACCP/SCCM consensus conference proposed that MODS be adopted to describe a process that was not only variable in its severity but potentially reversible following a period of organ system support.[4]

In contrast to SIRS, whose criteria define an appropriate and adaptive physiologic response, the development of organ dysfunction is always detrimental to the host. It is therefore appropriate to consider MODS as a syndrome—not a disease to be treated but an outcome to be prevented. The development of MODS invariably follows an acute threat to life that evokes the physiologic changes of systemic inflammation. MODS can be conceived as the maladaptive outcome of systemic inflammation, the syndrome that reflects the adverse consequences of a potentially life-preserving response. Such a model has important implications for clinical studies of therapies that can modify the expression of inflammation in the critically ill, as the objective of such interventions can be redefined as support of the beneficial aspects of inflammation and minimization of its maladaptive and detrimental consequences. It is of considerable importance therefore that the syndrome be defined optimally.

Approaches to the Description of MODS

If MODS is a syndrome, how should it be characterized? First, although a number of organ systems may show evidence of physiologic dysfunction in the critically ill, there is no convincing evidence to suggest that any particular pattern of organ system involvement characterizes the syndrome. Whereas pulmonary and hematologic dysfunction may arise in one patient, in another the predominant manifestations of organ dysfunction may be cardiovascular, hepatic, and renal dysfunction. It is generally assumed that the specific pattern of organ dysfunction per se has no diagnostic or prognostic significance. Rather, MODS is defined by the concurrence of dysfunction in two or more organ systems; and the severity of the physiologic derangement, rather than its pattern, carries the greatest prognostic importance. Thus descriptive systems for MODS uniformly omit the requirement for involvement of any given organ system but, rather, focus on the multiplicity of systems involved.

The organ systems whose dysfunction is considered to define MODS vary from one report to the next, but a systematic review of all published reports demonstrated that seven organ systems—respiratory, renal, hepatic, gastrointestinal, hematologic, cardiovascular, and neurologic—were included in at least half of all published studies.[38] On the other hand, systems such as the endocrine system[39,40] and the immune system,[41] whose functions can readily be shown to be deranged in critically ill patients, have rarely been included in descriptive reports of MODS. Their omission likely reflects the relative inaccessibility of measures of their dysfunction rather than a belief that this dysfunction portends a fundamentally different clinical process.

As important as the definition of the systems whose dysfunction defines MODS is identification of criteria that characterize dysfunction within a given organ system. In general terms, dysfunction can be defined by one of three approaches.

TABLE 2.1. Differences Between Organ Dysfunction Scales.

Variable	Approaches
Selection of variables	Physiologic variables only Combined physiologic and therapeutic variables
Variable describing cardiovascular dysfunction	Pressure-adjusted rate (Heart rate × CVP/MAP) Inotrope dose Blood pressure (elevation) Blood pressure, pH, fluid requirements)
Weighting of variables	Equal weighting based on independent contribution to ICU mortality Differential weighting based on aggregate contribution to mortality in logistic model
Value recorded	Worst values Representative value

CVP, central venous pressure; MAP, mean arterial pressure.

1. As a single variable that reflects a *physiologic derangement* (e.g., PO_2/FiO_2 ratio)
2. As a single variable that reflects a *therapeutic intervention* in response to a physiologic derangement (e.g., the need for mechanical ventilation)
3. As a combination of variables that in their own right define a *syndrome* (e.g., PO_2/FiO_2 ratio < 200, diffuse fluffy infiltrates on the chest radiograph, and a pulmonary capillary wedge pressure < 18, defining ARDS)

A series of properties of the optimal descriptor of organ dysfunction has been articulated[38] and forms the basis for one system that quantifies the severity of MODS as a score that measures the physiologic derangements of the syndrome.[42] A number of similar systems that measure organ dysfunction as an aggregate score have been proposed.[42–45] They differ in subtle but potentially important ways (Table 2.1), and further refinement of the descriptive process of MODS must focus on resolving or reconciling these differences.

Using Organ Dysfunction Scales to Describe the Course of Critical Illness

Organ dysfunction scores have been developed with the objective of describing the course of a critical illness, rather than predicting its outcome. Their use has been relatively limited to date, but the availability of validated and acceptable measures of organ dysfunction provides a tool that can serve a number of descriptive ends.[46]

Organ Dysfunction as a Risk Factor

The most powerful predictive tools are scoring systems such as APACHE[47] or the Simplified Acute Physiology Score (SAPS),[48] which have been developed to maximize their prognostic

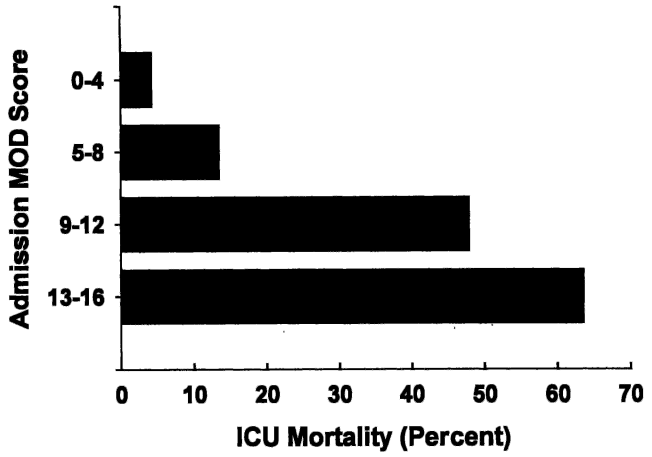

FIGURE 2.2. Severity of organ dysfunction on the day of ICU admission, as reflected in the multiple organ dysfunction (MOD) score, is strongly associated with the probability of ultimate ICU survival. Scores are the aggregate of representative values for dysfunction in each of six organ systems.[42] Data are from a study of 851 patients admitted to a surgical ICU.[49]

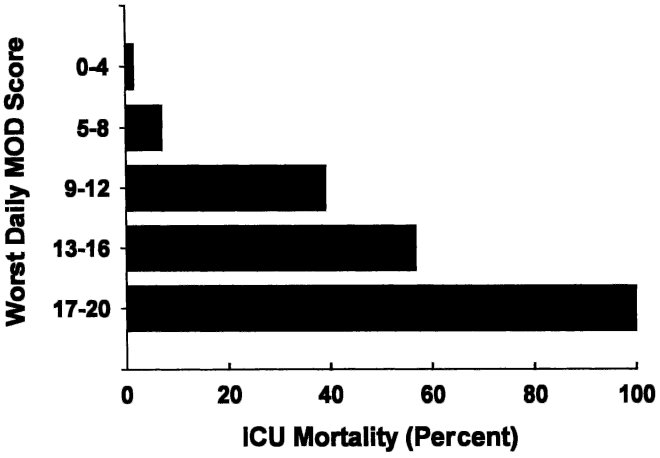

FIGURE 2.3. Severity of organ dysfunction occurring on a given ICU day correlates with the ultimate risk of ICU mortality. Such a point measure of illness severity can be followed to track the response to therapy, or it can be used as a surrogate for the intensity of resource utilization. (From Marshall et al.,[49] with permission.)

capabilities. Nonetheless, an organ dysfunction score that reflects increasing degrees of physiologic derangement early during the patient's clinical course score, by definition, can predict subsequent mortality.

Calculation of an organ dysfunction score on the day of ICU admission provides a measure of the severity of organ dysfunction at the onset of therapy. Such a measure can serve several purposes. As a baseline snapshot of illness severity, it provides the clinician with an indication of the extent of the patient's need for ICU support, which may aid in making decisions regarding staffing or resources and give an indication of the probability that such support will be successful (Fig. 2.2).[49] It cannot predict whether a given patient will live or die; but by providing an objective measure of the challenges faced and the expected outcome, it permits realistic discussions of the need for and limitations of therapy. Calculation of baseline organ dysfunction scores is of benefit for clinicians undertaking ICU research by defining an appropriate population for study (eliminating, for example, those who are either too well or too ill to benefit from therapy). Comparison of baseline scores provides a description of two or more study groups and permits comparison of their similarities and differences at baseline.

Organ Dysfunction as a Point Measure of Illness Severity

Calculating a score on any given day of ICU care provides a point measure of morbidity or illness severity. Such a measure can be followed serially to determine the clinical trajectory of an individual patient or a group of patients, or it can be calculated at a single point in time in a group of patients (e.g., 3 or 14 days after institution of therapy) to determine whether an intervention has altered outcome (Fig. 2.3). The worst single day's score can also be used as an outcome measure for a clinical trial. Although not explicitly evaluated as such, daily organ dysfunction scores may provide a point estimate of the intensity of resource utilization, analogous to the Therapeutic Intervention Scoring System (TISS).[50]

Organ Dysfunction as a Measure of Aggregate ICU Morbidity

An understanding of the clinical course of an ICU patient cannot adequately be derived from an evaluation of the status of that patient at a single point in time, even if that evaluation is done on the day the patient was most severely ill. By calculating an aggregate organ dysfunction score as the sum of the worst day's values for each isolated organ system, without reference to the day on which that value was obtained, the clinician can obtain a measure of the severity of illness over the entire ICU stay, a measure of global morbidity that occurs during an ICU admission. Such an approach has been taken by organ failure systems that quantify organ dysfunction as the number of failing systems.[34,51,52] A similar approach is readily used with an organ dysfunction score (Fig. 2.4). Aggregate scores may be calculated over any time period (e.g., the ICU stay, the duration of the administration of a novel therapeutic agent, or the same interval for which survival is being evaluated in a clinical trial.

Organ Dysfunction as an Aggregate Measure of Morbidity and Mortality

Organ dysfunction scores minimize the importance of death as an ICU outcome. Although the risk of death increases as the organ dysfunction score increases, it is possible for a given patient to die with a low score or a high score; and regardless of that value, the significance for the patient is the same. If, for example, a new therapy under investigation reduced the severity of organ dysfunction but resulted in an increased risk of fatal

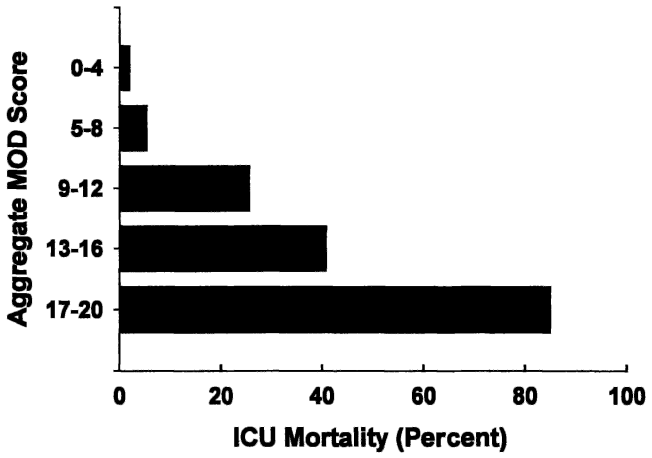

FIGURE 2.4. Aggregate scores are created by summing the worst daily value for each system, irrespective of whether those abnormalities occurred concomitantly or consecutively. They provide an aggregate measure of morbidity over time. The delta score, the difference between aggregate and admission scores, is a measure of morbidity specifically attributable to events occurring within the ICU. (From Marshall et al.,[49] with permission.)

cardiac dysrhythmias or myocardial infarction (complications for which scores would predictably be low), an organ dysfunction score might suggest benefit despite an increased mortality rate. The aggregate score described above can be adjusted to incorporate death as an outcome by assigning a maximal number of points to any patient who dies during the period of ascertainment. Such a mortality-adjusted score is a composite measure of both morbidity and mortality and has been used, for example, to demonstrate the detrimental consequences of transfusion above a trigger of 7 g/dl in critically ill patients.[53]

Measuring Change Over Time

These four basic models for the quantification of organ dysfunction permit the clinician to measure clinical change over time in a variety of ways. The difference between the aggregate score (with or without mortality adjustment) and the admission score (also known as the delta score) is a measure of organ dysfunction that arises after ICU admission and therefore is attributable to events occurring within the ICU and potentially modifiable through the institution of prophylactic or therapeutic measures. The delta score reflects that component of illness that is potentially modifiable and is therefore of particular interest to the physician. It can be calculated, for example, as an outcome measure in a clinical trial. Similarly, because it reflects new morbidity arising after the institution of ICU care, it can serve as a tool to identify cases for closer review for quality assurance processes. Regardless of the baseline severity of organ dysfunction, the risk of mortality in the ICU increases as the delta score increases, suggesting it is a sensitive surrogate outcome measure.

Delta scores can be calculated in other ways. A study of an intervention that may hasten the resolution of organ dysfunction could calculate the difference between baseline scores and the score at a predetermined interval following the resolution of therapy, or it could plot daily scores for two groups in a manner analogous to that used for plotting survival curves.

Conclusions

The ICU is unique in that it provides care for a group of patients who, if endogenous homeostatic processes had taken their normal course, would otherwise be dead. For illness of lesser gravity, survival in the absence of physiologic support is possible, and physiologic mechanisms have therefore evolved to maximize this probability. Evolutionary pressures have never had to contend with the array of interventions we routinely use to support the critically ill patient, and so it is hardly surprising that processes such as inflammation that are life-saving in their milder forms become part of a new problem to be solved in the highly artificial context of the ICU. Moreover, the boundaries of disease are blurred in a cohort of critically ill patients, and the very interventions used to support life become an intrinsic element of the pathologic processes that result in morbidity and death.[54]

The proliferation of acronyms to describe the course of critical illness reflects the efforts of intensivists to understand the complex interaction of disease, illness severity, and therapy that results in morbidity and mortality for the multiply-traumatized or critically ill patient. However, their articulation is a double-edged sword. By describing a process and defining boundaries for that process, the articulation of a new syndrome provides a basis by which workers can focus their investigations on subsets of patients or on a particular aspect of a series of complex physiologic interactions. The downside of such a process is the implicit assumption that by naming a process we have enhanced our understanding of it.

Certain critical care acronyms (e.g., CARS and MARS) describe concepts that have no defined correlate in clinical practice. Although they embody the biologic notion that activation of an inflammatory response is complex and includes intrinsic regulatory processes, they do not delineate a homogeneous group of patients in whom a consistent, unique biologic abnormality can be defined, or who can be shown to benefit from a particular therapeutic intervention. SIRS also defines a concept more than a syndrome, and it is only too well recognized that the criteria proposed for the syndrome lack the specificity necessary to differentiate patients with a disease from those with an appropriate, even pleasurable, physiologic response. The acronyms ARDS and MODS move closer to defining syndromes, as they are specific to processes in the critically ill, and their presence is always detrimental to the host. Their defining criteria remain frustratingly imprecise, however, and fail to discriminate homogeneous subpopulations of patients who might more appropriately be entered into trials of particular prophylactic or therapeutic strategies. The challenge facing critical care research is to move beyond concepts and syndromes to define discrete diseases of critical illness that reflect the derangement of a single, unique biologic process. Only then will we be able to move from nonspecific physiologic support to biology-based therapy.

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