3

ORGAN FAILURE

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> *The organism possesses certain contrivances by means of which the immune reaction, so easily produced by all lands of cells, is prevented from acting against the organism's own elements and so giving raise to autotoxins. Further investigations made by us have confirmed this view so that one might be justified in speaking of a "horror autotoxicus" of the organism. The formation of tissue autotoxins would, therefore, constitute a danger threatening the organism.*
>
> Ehrlich and Morgenroth (1901)

When challenged by an invading microorganism, such as a bacteria, a fungus or a virus, the human body starts a series of defense mechanisms, aimed at confining the invaders, controlling the damage and repairing the injured organs and tissues. Such a reaction, that involves a series of cells of the immune system and the liberation of pro and anti-inflammatory cytokines, is in most cases beneficial, allowing the survival of the patient with a minimum of residual injuries.

In some cases, due to poorly understood mechanisms, probably influenced by the type of microorganism involved [1], an imbalance occurs between the degree of injury and the host reaction, resulting in a process of generalized autodestructive inflammation with widespread tissue injury [2]. The clinical

manifestation of this process is the multiple organ dysfunction syndrome (MODS), also termed multiple organ failure (MOF) syndrome, the sequential and progressive dysfunction/failure of diverse organs and systems in an acutely ill patient such that homeostasis cannot be maintained without intervention [3].

The pathogenesis of this syndrome, that is responsible for a large number of deaths in critically ill patients, is still poorly understood. There are no doubts, however, that its incidence is increasing. An older population, at least in the western world, an increasing prevalence of chronic diseases, and a greater use of aggressive therapies all contribute to an increasing severity of illness in the patients admitted to general intensive care units (ICUs). The advances in our knowledge of the etiological and physiopathological mechanisms of severe diseases, and in the technologic possibilities for organ support also result in the initial survival of patients who, until a few years ago, would have died before reaching the hospital or within the first hours of hospital stay. MODS/MOF has emerged as one of the consequences of these advances. The initial survival of those patients, after severe insults, usually with very long stays in the ICU, results in an increasing number of complications during the ICU stay. At the same time, we still do not have any therapeutic approach to the status of immunological imbalance that is responsible, or at least occurs, in this syndrome. Consequently, our interventions are mainly preventive, trying to avoid the development of MODS/MOF and supporting homeostasis during the course of the disease. These factors result in considerable morbidity, mortality and resource consumption.

The objective of this chapter is to review the definition, epidemiology, and prognosis of MODS/MOF, with particular attention to sepsis and septic shock.

DEFINITION

Most of the patients with sepsis die in the ICU as a consequence of the sequential and progressive dysfunction/failure of several organs and systems, MODS [4-8]. Described initially by Tilney e al. after severe hemorrhage and shock in major aortic surgery [9], MODS/MOF was subsequently described in association with infection [10,11], acute pancreatitis [12], burns [13], shock [14] and trauma [15].

Over recent years, several definitions of MODS/MOF have been used. A consensus conference organized by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference in 1992, defined MODS as the presence of altered organ function in an acutely ill

patient such that homeostasis cannot be maintained without intervention [3]. The MODS was also divided into primary or secondary. In primary MODS, organ dysfunction occurs as the result of a well-defined direct insult in which organ dysfunction occurs early and can be directly attributable to the insult itself, such as acute renal failure due to rhabdomyolisis in trauma. In secondary MODS, the organ dysfunction/failure is not a direct consequence of the initial insult, but secondary to the host response to a primary insult such as infection. In this case, the generalized activation of the inflammatory cascade leads to the injury of normal tissues, remote from the initial site of injury.

In both cases, it should be noted that MODS/MOF represents a continuum of organ dysfunction, modulated by numerous factors at different time periods, both process and host related and in which changes in organ function over time are an important element in prognosticating the outcome of the syndrome.

EPIDEMIOLOGY

Sepsis and MOF represents the largest cause of mortality in the ICU [16-18]. Its increasing prevalence and the emergence of new pathogens has been related to changes in the characteristics of the populations and in the use of immunosuppressive therapies and invasive procedures [3]. We are currently treating older patients, with more severe underlying pathology and subjected to more aggressive therapy.

The relationship between the development of MODS/MOF and infection was postulated several years ago [10,11], alhough, only recently, has accurate data become available on the relationship between these two processes and on the magnitude of the phenomenon.

Bacteremic sepsis was, in 1997, the 12^{th} cause of death in the general population of the United States (US) [19], with an age-adjusted death rate of 4.2 cases per 100,000 standard population. This number is increasing, with a 2.4% increase from 1996 to 1997 and an 82.6% increase from 1979 to 1997. Sands et al. estimated that in large academic centers in the US, the incidence of sepsis was two cases per hundred hospital admissions, with more than 50% of all cases being admitted to the ICU [20].

In France, Brun-Buisson et al. [21], analyzing a large number of patients with the systemic inflammatory response syndrome (SIRS) admitted to 24 French hospitals, found incidence rates of bacteremia and of bacteremic severe sepsis of 9.8 and 2.6 per 1,000 adult admissions, respectively with rates 8 and 32 times higher in ICUs than in the wards. The probability of developing severe sepsis during bacteremia was higher in older patients, and

in those with infections of intraabdominal, pulmonary, neuromeningeal, and multiple sources. The development of severe sepsis presented a large impact on mortality, with mortality ranging from 29% in bacteremic patients to 54% in those with bacteremic severe sepsis.

Rangel-Frausto et al. [22], analyzing data from patients admitted to three ICUs in a University Hospital, found in 2527 patients with SIRS, that 48% of them developed the sepsis continuum (sepsis 26%, severe sepsis 18%, and septic shock 4%), with a very important mortality (sepsis 16%, severe sepsis 20% and septic shock 46%) [22]. The number of bacteremic patients increased when patients progressed from SIRS to sepsis, severe sepsis and septic shock (sepsis 17%, severe sepsis 25%, septic shock 69%). No differences in prognosis were evident between patients with bacteremic and non-bacteremic sepsis and septic shock. The number of failing organ/systems, defined as the occurrence of the adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), acute renal failure and shock increased when patients progressed from SIRS to sepsis, severe sepsis and septic shock. The same finding was demonstrated by Pittet et al. who found that, in ICU patients with sepsis and positive blood cultures, outcome is mainly determined by the severity of illness at ICU admission and preexisting comorbidities, the need for mechanical ventilation, hypothermia and previous antibiotic therapy at onset of sepsis and the number of vital organ dysfunctions developing subsequently [23].

In the EPIC study, published in 1995, based on data from 1417 ICUs in 17 Western European countries, Vincent et al. estimated that 44.8% of the patients were infected (20.6% with ICU acquired infection) [24]. Clinical sepsis was associated with a 3.5 odds-ratio for mortality. These results are similar to those described before by Parrillo et al. in 1990, who found that when sepsis develops, mortality is close to 30%, reaching 50% in septic shock and up to 80% in the MODS/MOF syndrome [25].

This issue was studied also by the Outcome and Prognosis Working Groups of the Portuguese Society of Intensive Care and the Portuguese Society of Internal Medicine [26]. In this study, in 15 Portuguese ICUs, infection was present on admission in 33.6% of the patients, and significantly associated with a higher age, greater severity of disease, a longer ICU stay and a greater ICU and hospital mortality. The amount of organ dysfunction/failure present at admission, as evaluated by the SOFA score, was significantly related to the presence of infection (Figure 1) and with the presence of criteria for sepsis and septic shock [3], both on admission and during the ICU stay. Mortality in the ICU and in the hospital was significantly related to the development of sepsis and septic shock (patients without criteria 12.3% and 14.3%; SIRS 18.6% and 26.8%; sepsis 27.3% and 39.8%; septic shock 41.7% and 58.0%, respectively).

A similar impact on mortality was demonstrated in a multicenter study promoted in 40 ICUs by Vincent et al., with ICU mortality ranging from 3.2% in patients that never developed an organ failure during ICU stay to 91.3% in patients that presented failure of the 6 analyzed organ/systems at any time during the ICU stay (Figure 2). An impact on ICU mortality was demonstrated also for minor degrees of organ dysfunction (Figure 3), and for the degree of organ dysfunction/failure appearing during the ICU stay (Figure 4) [27].

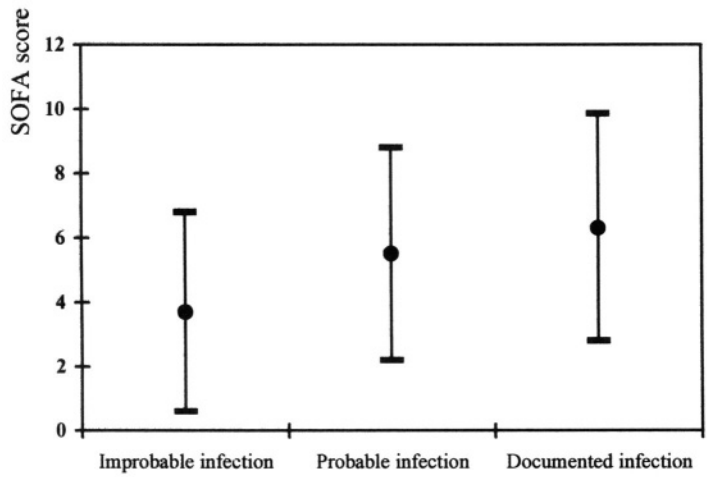

Figure 1. Admission sequential organ failure assessment (SOFA) score on admission to the ICU and presence of infection in 15 Portuguese ICUs. Results are presented as mean ± standard deviation. Adapted from [26].

These increases in the frequency and gravity were not accompanied by the emergence of new diagnostic or therapeutic approaches. After a decade of clinical trials with marginal or null results [28,29], mortality remains high, although some authors suggest a recent reduction [30]. It should be noted, however, that the absence of standard definitions for the definition of individual organ dysfunction/failure makes it almost impossible to compare different series. Also, most reports do not describe the presence and impact of other events in the evolution of the disease that influence the prognosis such as inadequate etiological treatment, late or inadequate surgery, and the appropriateness of concomitant therapeutics [31].

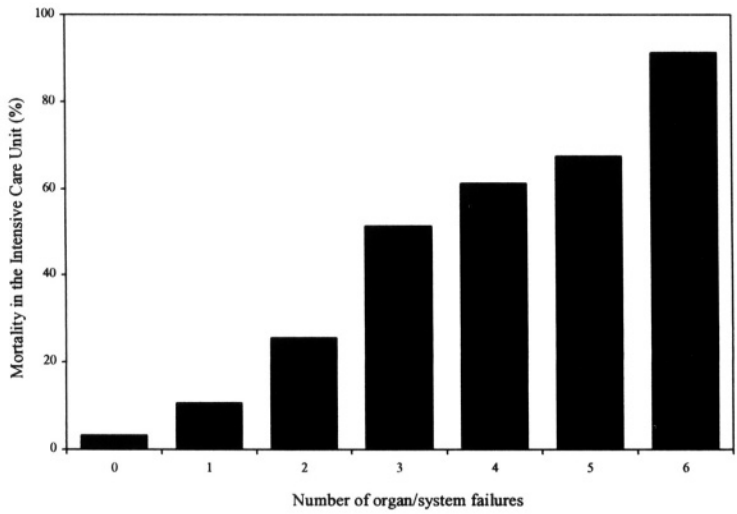

***Figure 2**. Maximum number of organ failures during the stay in the ICU and mortality. Organ failure was defined as the occurrence of a SOFA score ≥ 3. Adapted from [27].*

THE QUANTIFICATION OF MODS/MOF

Since the publication by Knaus et al. of an objective scale for the quantification of MOF [4], several such systems have appeared in the literature. The last published systems are the Multiple Organ Dysfunction score (MODS), by Marshall et al. [32], the Logistic Organ Dysfunction (LOD) score by Le Gall et al. [33] and the Sequential Organ Failure Assessment (SOFA) score, developed by a panel of experts of the European Society of Intensive Care Medicine [34].

All these systems have been developed in order to be:

- able to quantify the increasing dysfunction of individual organs, evaluating MODS/MOF as a continuum of dysfunction/failure instead of an on/off phenomena;
- applied sequentially, since MODS/MOF is a dynamic process and the degree of dysfunction varies with time;
- using objective variables, easy to collect and register, available in all ICUs, for the evaluation of each organ. They should be specific for the

analyzed organ and independent from baseline characteristics of the patients;

- independent from local variations in therapeutic approaches;
- designed to describe morbidity and not to predict mortality;
- allowing the individualization of individual organ function instead of aggregated physiological status.

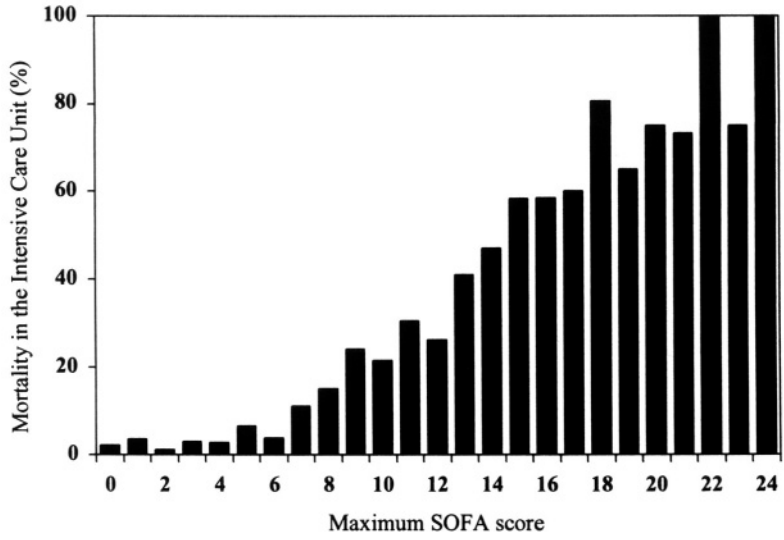

***Figure 3**. Maximum SOFA score during the ICU stay, and mortality. Adapted from [27]*

This process of sequential, repeated evaluation of the MODS/MOF is quite new in intensive care medicine, and there is no consensus about which organ/systems should be monitored and quantified, or which is the best system to use. Several such systems have been proposed in the past [2,4,10,32-41], differing among them in the type of variables used: physiologic and/or therapeutic (Table 1) [42,43]. Most of the scores analyze six organ/systems: respiratory, cardiovascular, renal, hematological, neurological and hepatic.

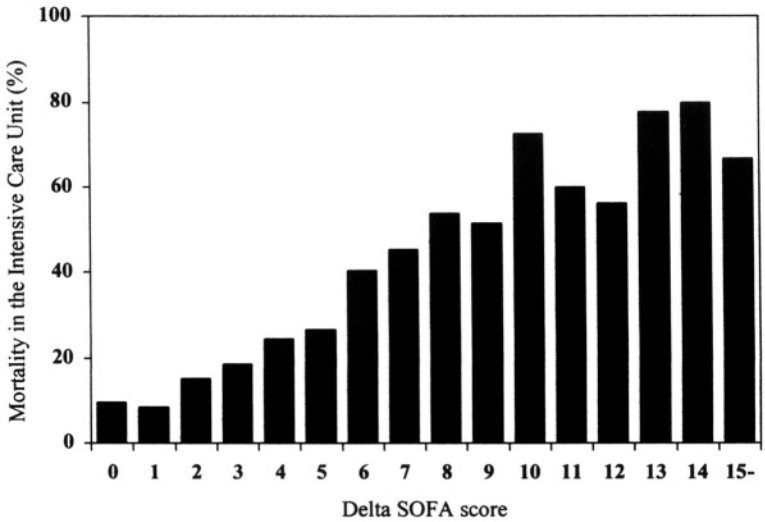

Figure 4. Delta SOFA score during the ICU stay, and mortality. Delta SOFA, the degree of organ dysfunction/failure appearing during the ICU stay, was computed as maximum SOFA minus admission SOFA score. Adapted from [27]

Organ System Failure (OSF) Score [4]

Published by Knaus et al. [4], the OSF score is the oldest of these systems in use. Describing MODS/MOF as a binary phenomenon (absent/present), it does not allow the quantification of smaller degrees of organ dysfunction. It should be applied daily, in consecutive periods of 24 hours, during the whole ICU stay. An extensive revision of the OSF was published recently by Zimmerman et al. [44], suggesting that mortality from MOF has decreased in recent years [45].

The OSF originally evaluated five organs/systems: respiratory, cardiovascular, renal, hematological, and neurological. Some modifications have been published, such as that by Garden et al., which added hepatic failure [46].

Organ/system	Physiologic variables	Therapeutic variables
Respiratory	PaO_2/FiO_2	Mechanical ventilation Level of PEEP
Cardiovascular	Blood pressure	Use of vasoactive drugs
Renal	Urinary output Blood urea Blood creatinine	Dialysis
Hematological	Platelets Leucocytes Hematocrit	Use of blood
Neurological	Glasgow coma score	Use of sedative drugs

PEEP: Positive pressure at end-expiration

Table 1. Types of variables used in multiple organ dysfunction/failure systems. Adapted from [71].

Multiple Organ Dysfunction Score (MODS) [32]

The MODS score was described in 1995 by Marshall et al [32]. Developed after an extensive critical review of the literature, it was later tested and validated in a sample of surgical critically ill patients. This system was subject recently to an external validation in patients with septic shock, revealing a good behavior in medical and surgical patients [47].

The MODS analyzes six organ/systems, assigning from 0 (normality) to 4 (failure) points to each of them: respiratory, renal, hepatic, cardiovascular, hematological and neurological, for a maximum of 24 points. The worst values for each organ or system in a certain period of 24 hours are added later for the calculation of total MODS score in a certain day.

This system differs significantly from the other modem systems in the method chosen for assessing the cardiovascular system. While in the other systems a group of physiologic and/or therapeutic parameters is evaluated, in MODS the evaluation of the cardiovascular dysfunction/failure is given by a composed variable, the pressure-adjusted heart rate (PAR). This fact leads to a more complex calculation, although it presents an excellent discriminative capability when compared with the other systems [48].

It was demonstrated that this system presents a better discriminative capacity than APACHE II or daily OSF [47] and it has been used in several studies [49-52].

Logistic Organ Dysfunction (LOD) System [53]

Proposed by Le Gall et al. [53], this system was developed with the use of complex statistical techniques to choose and weight the variables in a large sample of critical ill patients. The database used (the same as that used for the development of the SAPS II and MPM II) only had data collected during the first 24 hours of ICU stay, and no information exists about its performance later during the ICU stay.

The LODS comprises six organ/systems: neurological, cardiovascular, renal, respiratory, hematological and hepatic and it is the only one of the systems published to allow the calculation of the probability of hospital mortality, based on the amount of dysfunction/failure present at 24 hours on the ICU.

For the computation of the score, each organ or system receives a growing value between 0 and 5 points, this last possible of being just reached for the cardiovascular, neurological and renal systems (for the respiratory and hematological systems the maximum is 3 and for the hepatic system the maximum is 1). Maximum score is 22 points. All the variables should be measured at least once. The chosen value is the most abnormal in the period of 24 hours, missing values being considered normal for the calculation of the score.

In preliminary analyzes the LODS seems to present a deficient calibration and a lower discriminative capability than the other systems [48]. It has been used to date in just one published study [54], although it was the chosen system for European Sepsis Project, recently ended.

Sequential Organ Failure Assessment (SOFA) Score [34]

Developed in 1994 by a panel of experts of the European Society of Intensive Care (ESICM), based on a revision of the literature, the SOFA score was originally denominated sepsis-related organ failure assessment score.

The SOFA quantifies the dysfunction/failure of six organ/systems: respiratory, hematological, hepatic, cardiovascular, neurological and renal, punctuated from 0 (normal function) up to 4 points (severe failure). It presents therefore a maximum score of 24 points.

The SOFA has been validated in several contexts, presenting a good behavior in unselected critically ill patients [55], and in patients with trauma [56], renal failure [57], and cardiovascular disorders [58]. Recently we published derived measures based on this system, destined to a more detailed evaluation of the evolutionary patterns of the critically ill patient [27]. The SOFA has been used in several clinical studies [58-62].

Not all Organs are Created Equal

Maximum organ dysfunction/failure is usually reached soon after ICU admission, although some differences exist among the different organ and systems. In the ESICM study [27], the mean time to reach maximum failure in patients with organ failure **(SOFA score ≥ 3 points)** was **2.9 ± 1.1** days, ranging from 1.6 days for the neurological score to 4.9 for liver failure (Table 2).

Organ/System	Days in the ICU
Respiratory	2.33 (2.03 – 2.63)
Cardiovascular	2.54 (2.09 – 2.98)
Renal	2.75 (2.10 – 3.41)
Hematological	3.09 (2.38 – 3.80)
Hepatic	4.90 (3.91 – 5.89)
Neurological	1.57 (1.23 – 1.91)

***Table 2**. Time to reach maximum organ failure in patients with organ failure (SOFA score ≥ 3). Values are presented as mean (95% confidence interval for the mean). Adapted from [27].*

The cardiovascular score was associated with the highest relative contribution to outcome (odds-ratio for a one point change in the score 1.68, 95 % confidence interval 1.49 to 1.91), followed by the renal (odds-ratio 1.46, 95 % confidence interval 1.29 to 1.64), the neurological (odds-ratio 1.40, 95 % confidence interval 1.28 to 1.55), the coagulation (odds-ratio 1.22, 95 % confidence interval 1.06 to 1.40) and the respiratory (odds-ratio 1.18, 95 % confidence interval 1.01 to 1.38) scores. No such contribution could be

demonstrated for the hepatic score (odds-ratio 0.82, 95 % confidence interval 0.60 to 1.11). These findings corroborate what is known about the importance of hemodynamic derangements in sepsis [63]. This differential contribution to outcome of the several organ/systems is taken into account only by the LOD score.
The best discriminative power was shown for the cardiovascular score (are under ROC curve 0.802, standard error (SE) 0.015), the renal score (0.739, SE 0.016) and the respiratory score (0.736, SE 0.016). For the neurological score the value was intermediate (0.727, SE 0.016). Coagulation (0.684, SE 0.018) and hepatic scores (0.655, SE 0.019) had a lower discriminative power. The aggregated score (total maximum SOFA score) presented an area under ROC curve of 0.847 (SE 0.012) which was significantly higher (cardiovascular score $p = 0.005$, all others $p < 0.001$) than any of its individual components.

Which System to Use?

The systems for the quantification of MODS/MOF differ mainly in the way they evaluate the cardiovascular system: the SOFA score uses the mean blood pressure and the level of vasoactive support, the LOD score the systolic blood pressure and the heart rate and the MODS a composed variable, the pressure-adjusted heart rate(PAR). The only formal comparison among them, published as abstract, seems to indicate a better discriminative capability for MODS and of the SOFA systems than for LOD [48]. However, the low number of analyzed patients requires additional confirmation of these findings from other studies. From a theoretical point of view, the LOD score presents the advantage to assigning different points to different organ/systems based on empirical data, with ranges defined by multiple logistic regression.

The main similarities and differences among these methods are described in Table 3.

Currently, and in the absence of better recommendations, each ICU should use the system that:

- is tested and validated in their population;
- results in the smallest percentage of missing values;
- is least time-consuming to register and compute.

Comparative to the general outcome prediction models, these systems are an important part in our evaluation of the critically ill patient, since they describe better the evolution of the individual patient and are more sensitive to changes due to the evolution of the disease, to the response to therapy or to the emergence of complications.

It should be noted that, independent of the system used, several doubts remain about their sensitivity, the best endpoint to be used in their evaluation (ICU versus hospital mortality), the best time to start evaluation (ICU admission versus start of the septic process) or their incorporation in more general systems (such as the daily APACHE II adjusted for organ-failure [37]).

Organ/system	SOFA [34]	MODS [32]	LOD [33]	OSF [4]
Respiratory	PaO_2/FiO_2 ratio Mechanical ventilation	PaO_2/FiO_2 ratio	PaO_2/FiO_2 ratio Mechanical ventilation	Respiratory rate $PaCO_2$ $AaDO_2$ Mechanical ventilation > 72 hours
Cardiovascular	Mean blood pressure Use of vasoactive agents	PAR	Systolic blood pressure Heart rate	Heart rate Mean arterial pressure Ventricular tachicardia Ventricular fibrillation pH
Renal	Creatinine Urinary output	Creatinine	Creatinine Urea Urinary output	Urinary output Urea Creatinine
Hematological	Platelets	Platelets	Leucocytes Platelets	Leucocytes Platelets Hematocrit
Neurological	Glasgow coma score	Glasgow coma score	Glasgow coma score	Glasgow coma score
Hepatic	Bilirubin	Bilirubin	Bilirubin Protgrombin time	---

$AaDO_2$: alveolo-arterial diference in oxigen; PAR: pressure-adjusted heart rate

Table 3. *Comparison of the variables used in the systems for the quantification of MODS/MOF*

The Application of MODS/MOF systems

The systems for the quantification of MODS/MOF are destined to the description of the critically ill patient. Several aggregated measures have been proposed for this effect [27,64,65]. The most important are:

- Admission score: reflects the condition of the patient at ICU admission. Depends basically on the pre-ICU care and admission policies of each ICU, allowing the quantification of the severity at

admission. It can be used for instance as an entry criterion in clinical studies or to evaluate the baseline comparability of groups in clinical trials;

- Daily score: sum of the individual scores for the several organ/systems in a certain day. Evaluates therefore the degree of dysfunction/failure on a certain day. It is especially useful when analyzed in a serial way to monitor the evolution of a certain patient;
- Delta score: the difference between the maximum score and the admission score. Reflects the degree of dysfunction/failure that appears after admission in the ICU, being especially useful to monitor the impact of events occurring after ICU admission, such as the development of nosocomial infection;
- Total maximum scores: is the sum of the scores for each organ or appraised system during the whole ICU stay. Reflects the cumulative insult suffered by the patient, taking into consideration that the dysfunctions/failures of the organ systems appear in different periods of time;
- Organ failure free days: computed for a certain organ, counting, in a certain period of time (usually 28 days), the number of days in which that the patient was alive and without failure of the respective organ. It is especially useful for combining a measure of the morbidity of the surviving patients and of the mortality in the patients who died.

CONCLUSION

MODS/MOF continues to be associated with a poor survival rate. We are still unable to treat etiologically MODS/MOF or, at least, to modulate the immunological mechanisms underlying its installation and progression. Consequently, our best weapon to fight this disease is prevention. Unfortunately, this is not possible in many cases.

While we wait for the physiologists, immunologists, and geneticists to return from the drawing board, as Chernow once said [66], our clinical efforts should be directed especially at the early detection and treatment of sepsis and infection. Early diagnosis and the start of effective antimicrobial therapy have been proven to be associated with a better outcome [67-69]. Krager et al. demonstrated more than 20 years ago that appropriate antibiotic treatment reduced the fatality rate in patients with bacteremia by approximately 50% [67]. Additionally, they shown that early appropriate antibiotic therapy also reduced the frequency with which shock developed by 50%. Even after the development of shock, appropriate antibiotic therapy significantly reduced fatality rates. These are clinical lessons so often forgotten by those more

concerned with microbial ecology and cost-saving at any price than with the lives of the human beings, critically ill, that are in our ICUs. Special attention should also be given to early surgery, aimed at the drainage of septic focus. As someone once said "there is no good medicine for bad surgery". Other factors are also probably important, such as the way we feed our patients [70].

All these factors should be taken into account and incorporated in future systems for risk stratification and description of septic patients. We need to learn better how to monitor our patients, how to decide in whom, and when, we must start anti-inflammatory therapy and in whom, and when, we must start immunostimulating therapy. In this complex decision-making process, instruments such as the organ dysfunction/failure scores will be certainly helpful.

Finally, it is very important to use standardized language, following the advice of Lewis Carroll "When I use a word, it means just what I choose it to mean – neither more or less" (Lewis Carroll, Alice's Adventures in Wonderland & Through the Looking Glass, 1965). If we look at the plethora of names we have been using in the past 30 years to describe this syndrome (sequential system failure; multiple, progressive, or sequential systems failure; multiple organ failure; multiple-systems organ failure; post-traumatic syndrome; hypermetabolism organ failure complex; gut origin septic state; multiple organ system failure; syndrome de insuficiencia multiple de organos y sistemas; multiple organ injury syndrome; post-traumatic organ system infection syndrome; multiple organ dysfunction syndrome), this is not what we have been doing.

REFERENCES

1. Opal SM, Cohen J. Clinical Gram-positive sepsis: does it fundamentally differ from Gram-negative bacterial sepsis? Crit Care Med 1999; 27:1608-1616
2. Goris RJA, te Boekhorst TP, Nuytinck JKS, Gimbrère JSF. Multiple-Organ Failure. Generalized autodestructive inflammation? Arch Surg 1985; 120:1109-1115
3. Members of the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions of sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-874
4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg 1985;202:685-693
5. Deitch EA. Multiple organ failure: pathophysiology and potential future therapy. Ann Surg 1992; 216:117-14
6. Tran DD. Age, chronic disease, sepsis, organ system failure and mortality in the elderly admitted to the intensive care medicine. Intensive Care Med 1994; 20:S110 (Abst)

7. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction. JAMA 1994; 271:226-233
8. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathofenesis of the disease process. Chest 1997; 112:235-243
9. Tilney NL, Baily GL, Morgan AP. Sequential system failure after rupture of abdominal aortic aneurisms: an unsolved problem in postoperative care. Ann Surg 1973; 178:117-122
10. Fry DE, Pearlstein L, Fulton RL, Polk HC. Multiple system organ failure. The role of uncontrolled infection. Arch Surg 1980;115:136-140
11. Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:293-298
12. Tran DD, Cuesta MA. Evaluation of severity in patients with acute pancreatitis. Am J Gastroenterol 1992; 87:604-608
13. Marshall WG, Dimick AR. Natural history of major burns with multiple subsystem failure. J Trauma 1983; 23:102-105
14. Henao FJ, Daes JE, Dennis RJ. Risk factors for multiorgan failure: a case-control study. J Trauma 1991; 31:74-80
15. Faist E, Baue AE, Dittmer H, Heberer G. Multiple organ failure in polytrauma patients. J Trauma 1983; 23:775-787
16. Manship L, McMillin RD, Brown JJ. The influence of sepsis and multisystemic organ failure on mortality in the surgical intensive care. Ann Surg 1984; 50:94-101
17. Niederman MS, Fein AM. Sepsis syndrome, the adult respiratory distress syndrome, and nosocomial pneumonia: a common clinical sequence. Clin Chest Med 1990; 11:633-650
18. Bernard G. Sepsis trials. Intersection of investigation, regulation, funding, and practice. Am J Respir Crit Care Med 1995; 152:4-10
19. Centers for Disease Control. Mortality patterns - United States 1997. Morb Mortal Wkly Rep 1999; 48:664-668
20. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. Academic Medical Center Consortium Sepsis Project Working Group. JAMA 1997;278:234-40.
21. Brun-Buisson C, Doyon F, Carlet J. Bacteremia and severe sepsis in adults: a multicenter prospective survey in ICUs and wards of 24 hospitals. French Bacteremia-Sepsis Study Group. Am J Respir Crit Care Med 1996; 154:617-624
22. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995; 273:117-23
23. Pittet D, Thiévent B, Wenzel RP, Li N, Auckenthaler R, Suter PM. Bedside prediction of mortality from bacteriemic sepsis. A dynamic analysis of ICU patients. Am J Respir Crit Care Med 1996; 153:684-693
24. Vincent J-L, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA 1995; 1:639-644
25. Parrillo JE, Parker MM, Natanson C, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 1990; 113:227-242
26. Moreno R, Matos R, Fevereiro T, Pereira ME. À procura de um índice de gravidade na sépsis. Rev Port Med Intensiva 1999; 8:43-52
27. Moreno R, Vincent J-L, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Intensive Care Med 1999; 25:686-6%
28. Eidelman LA, Sprung CL. Why have new therapies for sepsis not been developed? Crit Care Med 1994; 22:1330-1334

29. Bone RC. Why sepsis trials fail. JAMA 1996; 276:565-566
30. Friedman G, Silva E, Vincent J-L. Has the mortality of septic shock changed with time? Crit Care Med 1998; 26:2078-2086
31. Sprung CL, Finch RG, Thijs LG, Glauser MP. International sepsis trial (INTERSEPT): role and impact of a clinical evaluation committee. Crit Care Med 1996; 24:1441-1447
32. Marshall JC, Cook DA, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995; 23:1638-1652
33. Le Gall JR, Klar J, Lemeshow S, et al. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. JAMA 1996; 276:802-810
34. Vincent J-L, Moreno R, Takala J, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22:707-710
35. Elebute EA, Stoner HB. The grading of sepsis. Br J Surg 1983;70:29-31.
36. Stevens LE. Gauging the severity of surgical sepsis. Arch Surg 1983; 118:1190-1192
37. Chang RW, Jacobs S, Lee B. Predicting outcome among intensive care unit patients using computerised trend analysis of daily Apache II scores corrected for organ system failure. Intensive Care Med 1988; 14:558-566
38. Meek M, Munster AM, Winchurch RA, et al. The Baltimore Sepsis Scale: measurement of sepsis in patients with burns using a new scoring system. J Burn Care Rehabil 1991;12:564-568
39. Baumgartner JD, Bula C, Vaney C, et al. A novel score for predicting the mortality of septic shock patients. Crit Care Med 1992; 20:953-960
40. Fagon J-Y, Chastre J, Novara A, Medioni P, Gilbert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. Intensive Care Med 1993; 19:137-144
41. Bernard GR, Doig BG, Hudson G, et al. Quantification of organ failure for clinical trials and clinical practice. Am J Respir Crit Care Med 1995; 151:A323 (Abst)
42. Bertleff MJ, Braining HA. How should multiple organ dysfunction syndrome be assessed? A review of the variations in current scoring systems. Eur J Surg 1997; 163:405-409
43. Marshall JD, Bernard G, Le Gall J-R, Vincent J-L. The measurement of organ dysfunction/failure as an ICU outcome. Sepsis 1997; 1:41
44. Zimmerman JE, Knaus WA, Sun X, Wagner DP. Severity stratification and outcome prediction for multisystem organ failure and dysfunction. World J Surg 1996; 20:401-405
45. Zimmerman JE, Knaus WA, Wagner DP, Sun X, Hakim RB, Nystrom P-O. A comparison of risks and outcomes for patients with organ failure: 1982-1990. Crit Care Med 19%; 24:1633-1641
46. Garden OJ, Motyl H, Gilmour WH, Utley RJ, Carter DC. Prediction of outcome following acute variceal haemorrhage. Br J Surg 1985; 72:91-95
47. Jacobs S, Zuleika M, Mphansa T. The multiple organ dysfunction score as a descriptor of patient outcome in septic shock compared with two other scoring systems. Crit Care Med 1999; 27:741-744
48. Moreno R, Pereira E, Matos R, Fevereiro T. The evaluation of cardiovascular dysfunction/failure in multiple organ failure. Intensive Care Med 1997; 23:S153 (Abst)
49. Gonçalves JA, Hydo LJ, Barie PS. Factors influencing outcome of prolonged norepinephrine therapy for shock in critical surgical illness. Shock 1998; 10:231-236
50. Maziak DE, Lindsay TF, Marshall JC, et al. The impact of multiple organ dysfunction on mortality following ruptured abdominal aortic aneurysm repair. Ann Vasc Surg 1998; 12:93-100
51. Pinilla JC, Hayes P, Laverty W, et al. The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction. Surgery 1998; 124:799-805

52. Staubach KH, Schroder J, Stuber F, et al. Effect of pentoxifylline in severe sepsis: Results of a randomized, double-blind, placebo-controlled study. Arch Surg 1998; 133:94-100
53. Le Gall J-R, Klar J, Lemeshow S. How to assess organ dysfunction in the intensive care unit? The logistic organ dysfunction (LOD) system. Sepsis 1997; 1:45-47
54. Soufir L, Timsits JF, Mahe C, et al. Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: a matched, risk-adjusted, cohort study. Infect Control Hosp Epidemiol 1999; 20:396-401
55. Vincent J-L, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicentric, prospective study. Crit Care Med 1998; 26:1793-800
56. Antonelli M, Moreno M, Vincent J-L, et al. Application of SOFA score to trauma patients. Intensive Care Med 1999; 25:389-394
57. Mendonça A, Vincent J-L, Suter PM, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26:915-921
58. Janssens U, Graf C, GGraf J, et al. Evaluation of the SOFA score: a single center experience of a medical intensive care unit in 303 consecutive patients with predominantly cardiovascular disorders. Intensive Care Med 2000; 26:1037-1045
59. Di Filippo A, De Gaudio AR, Novelli A, et al. Continuous infusion of vancomycin in methicillin-resistant staphylococcus infection. Chemotherapy 1998; 44:63-68
60. Fiore G, Donadio PP, Gianferrari P, et al. CVVH in postoperative care of liver transplantation. Minerva Anestesiol 1998; 64:83-87
61. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999; 27:723-732
62. Hynninen M, Valtonen M, Markkanen H, et al. Interleukin 1 receptor antagonist and E-selectin concentrations: a comparison in patients with severe acute pancreatitis and severe sepsis. J Crit Care 1999; 14:63-68
63. Marik PE, Varon J. The hemodynamic derangements in sepsis. Implications for treatment strategies. Chest 1998; 113:854-860
64. Bernard GR. Quantification of organ dysfunction: seeking standardization. Crit Care Med 1998; 26:1767-1768
65. Marshall J. Charting the course of critical illness: prognostication and outcome description in the intensive care unit Crit Care Med 1999; 27:676-678
66. Chernow B. Back to the drawing board. Crit Care Med 1996; 24:1097-1098
67. Kreger BE, Craven DE, McCabe WR. Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. Am J Med 1980; 68:344-355
68. Bryan CS, Reynolds KL, Brenner ER. Analysis of 1186 episodes of gram-negative bacteremia in non-university hospitals: the effects of antimicrobial therapy. Rev Infect Dis 1983; 5:629-638
69. Weinstein MP, Murphy JR, Reller LB, Lichtenstein KA. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference bto factors influencing prognosis. Rev Infect Dis 1983; 5:54-70
70. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. Crit Care Med 1999; 27:2799-2805
71. Marshall JD, Bernard G, Le Gall J-R, Vincent J-L. Conclusions. Sepsis 1997; 1:55-57