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EDITORIALS

The role of evidence-based medicine in the management of critically ill patients

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ABSTRACT

Evidence-based medicine (EBM) is the most important strategy for assessing the vast amounts of available data and applying them appropriately to patients, especially in critical care field. However, in intensive care medicine, there is a short history of randomized controlled trial evidence to support therapeutic decisions and, only in the last years, several clinical trials have demonstrated positive results for different clinical interventions. In this article we will try to outline the principal therapeutic recommendations sustained by evidence-based medicine in critical care.

Key words: evidence based medicine; intensive care; sepsis

I. INTRODUCTION

The medical care has suffered tremendous progresses in the past decades and has become extremely complex thus the evaluation of diagnostic and therapeutic procedures has become increasingly difficult. We are currently facing an unprecedented information explosion that overpasses the individual capacity to assimilate. Each year, more over 4000 specialized articles are published and the modern physician has access to huge data bases.

This undoubtedly positive phenomenon carries several risks. Numerous therapeutic procedures, pharmacological or non-pharmacological, have entered medical practice due to promising mechanisms of action and have subsequently proved to be ineffective or dangerous. Thus, physicians are facing the risk of chaotic multi-drug prescribing, the medical practice lacks standardization and the costs of medical care increase. Furthermore, simple, cause-effect type studies, such as treating an infection with an antibiotic, are not possible today, due to complexity of current medical activity.

All these have imposed the development of a scientific approach aimed at analyzing and comparing as objectively as possible the diversity of diagnostic and therapeutic means, in order to establish their value, clinical utility and economic consequences. This is the principle behind the concept of "Evidence-Based Medicine" (EBM). EBM has entered in use 20 years ago and has greatly developed in the past decade, labeled as the "EBM era". This notion is defined as the analysis of effect on outcome of various diagnostic and therapeutic

procedures, using best scientific methods available: randomized clinical trials (RCTs), considered the golden standard, followed with great accuracy by meta-analyses of clinical studies.

EBM fulfills several needs of medical practice: the confirmation of a drug or intervention effects using multicentric, collective results, the testing of clinical effectiveness of therapies with promising mechanisms, and the comparison of different therapeutic alternatives.

EBM has proved to be superior to other approaches, such as personal experience, application in practice of experimental data, etc., that can lead to unsatisfactory or even dangerous results. Such an example is the use of antiarrhythmic drugs encainide, flecainide or moricizine in patients with ventricular premature beats in whom these drugs surprisingly increased mortality (1). Furthermore, the use of growth hormone in hypercatabolic patients did not improve outcome, on the contrary it increased mortality (2).

From the practical point of view, EBM is the layout for diagnostic and therapeutic guidelines and protocols that transfer into practice the results of clinical trials. EBM promotes the research, analysis of cost-effectiveness, limits the variations in medical practice and, last but not least, it has proved to be life-saving.

Despite undeniable qualities of EBM, several controversies persist, especially in the field of intensive care medicine. The heterogenity of patients included in clinical trials, most of all in the intensive care, is one major problem. Critically-ill patients are characterized by complex pathology and treatment, important variations of clinical status; all these are barriers to performance of clinical studies. It is difficult to estimate the influence of a single diagnostic or therapeutic method, as their use can be complex or may lead to erroneous interpretations.

The use of too tight inclusion criteria can lead to results that are not applicable to patients in clinical practice, who are often outside these criteria. Moreover, restrictive inclusion criteria impede on including a sufficient number of patients and the study results will fail to reach scientific significance. On the other hand, loose inclusion criteria carry the risk of false negative or negative results (3).

The performance of multicentric clinical trials is a very complex and difficult process, long and very expensive and that makes it impossible to repeat them, even when the results are not very clear. Furthermore, the publishing process is time-consuming, and it has been noted that there is a tendency to preferentially publish studies with positive results and that generates discussions on whether these data are valid (4).

Meta-analyses are another EMB-specific method. Many times the results of meta-analyses are disputable as they include inhomogeneous studies, with different levels of accuracy. A good explanation is the meta-analysis regarding the use of albumin in critically-ill patients with results that were not confirmed by subsequent studies (5).

Despite all these critics, EBM remains the method with the widest acceptance for transposing research into medical practice and for standardization of medical care. The results of randomized clinical trials have a significant influence on the medical community.

Of course, one can say that EBM cancels the role of clinical observation and personal experience, of physical examination and of the relationship between physician and the patient, but the art of medicine is exactly the ideal use of these valuable tools in order to reach the best solutions for our patients.

EBM has had a major impact on the medical care in intensive care units in the past years. Several clinical trials and meta-analyses have determined the introduction of new therapies or changed treatment strategies, with significant improvement of the outcomes. Most of these therapies are focused on at sepsis patients, but some address a larger group. Of course, the list is not exhaustive, and the fact that these therapies are considered "evidence-based" does not rule out the numerous controversies that accompany them. ❑

II. EARLY GOAL DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Sepsis represents the inflammatory response syndrome to infection. The heterogeneity of this syndrome's definition criteria has lead to the 1991 Consensus Conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM)

with the goal of standardizing the sepsis terminology (6).

Systemic Inflammatory Response Syndrome (SIRS) stands for the inflammatory response to various aggression factors and is defined by the presence of at least two of the following criteria: body temperature >38°C or <36°C, tachycardia (>90 beats/min), high respiratory rate (>20 breaths/min) or PaO_2<32 mmHg, WBC>12,000/mm^3, <4,000/mm^3 or >10% immature forms.

Sepsis is defined as SIRS with an associated of documented infection.

Severe sepsis represents sepsis with an associated organ dysfunction, hypoperfusion, perfusion disturbances or hypotension (clinically seen as lactic acidosis, oliguria or mental status alterations).

Septic shock is a form of severe sepsis characterized by hypotension despite proper volume resuscitation.

Because of its continuously growing incidence, the very high costs of treatment and the high mortality rate, sepsis became a major public health issue (7,8).

With sepsis being a continuous condition, with rapid progress towards aggravation and with early treatment being an important factor, Rivers et al. published in 2001 the results of a randomized clinical trial (RCT) including patients with severe sepsis or septic shock who were treated either in a standard manner (the objectives being a central venous pressure of 8-12 mmHg, a mean arterial pressure > 65 mmHg and an urine output > 0.5 ml/kg/h), or with the so called Early Goal Directed Therapy (EGDT) (9). Another goal was added to the treatment of the EGDT group, besides the standard therapeutically objectives: the maintenance of a central venous oxygen saturation in the venous blood of the superior vena cava (ScvO2) of at least 70%. Experts see this measurement (which only needs a common central venous catheter insertion) as equivalent to the measurement of the mixed venous oxygen saturation (which needs a more invasive procedure like Swan-Ganz catheter). Besides the standard fluid resuscitation therapy, oxygenation and vasoactive drugs, in the EGDT group, the $ScvO_2$ was maintained ≥ 70% with additional fluid administration, blood transfusions for achieving a haematocrit ≥ 30% and dobutamine.

Statistics showed that during the first 6 hours, the quantity of administered fluids was significantly greater in the EGDT group (4.981 ml vs. 3.499 ml), as were blood transfusions and dobutamine, and there was no difference in the number of patients needing ventilatory support and vasoactive drugs between the two groups. During the time period of 7 to 12 hours, the amount of i.v. fluids and transfusions was smaller in the EGDT group, as was the incidence of mechanical ventilation, vasoactive support and invasive hemodynamic monitoring. Overall, during the first 72 hours there were no differences between the two study groups regarding fluid and dobutamine administration, but there was a greater amount of blood transfusions in the EGDT group and a significantly lower need for mechanical ventilation, vasopressors and invasive monitoring using pulmonary catheters (9).

The impact on the outcome was remarkable, in hospital mortality being significantly lower in the EGDT group (30.5% vs. 46.5%).

Inevitably, these results raised great controversies, especially regarding the leading factor to lower mortality rates ($ScvO_2$ monitoring, aggressive volemic resuscitation, blood transfusions or dobutamine) (10) and the importance of the infused fluid types (11).

Regardling the differences in interpretation of the results, the main conclusion is the need of a rapid resuscitation of the patient with severe sepsis. The "Surviving Sepsis Campaign", a referring guide for the management of severe sepsis and septic shock set up in 2003 by experts representing 12 prestigious international organizations, considers EGDT as extremely useful and recommends it (grade B of evidence). We will reproduce this algorithm in the next paragraph:

"1. The resuscitation of a patient in severe sepsis or sepsis-induced tissue hypoperfusion (hypotension or lactic acidosis) should begin as soon as the syndrome is recognized and should not be delayed pending ICU admission. An elevated serum lactate concentration identifies tissue hypoperfusion in patients at risk who are not hypotensive. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol: central venous pressure: 8-12 mm Hg; mean arterial pressure ≥65 mm Hg; urine output ≥0.5 mL/kg/hr; central venous (superior vena cava) or mixed venous oxygen saturation ≥70% (grade B recommendation).

2. During the first 6 hrs of resuscitation of severe sepsis or septic shock, if central venous oxygen saturation or mixed venous oxygen saturation of 70% is not achieved with fluid resuscitation to a central venous pressure of 8-12 mm Hg, then transfuse packed red blood cells to achieve a hematocrit of ≥30% and/or administer a dobutamine infusion (up to a maximum of 20 microg/kg /min) to achieve this goal. (grade B recommendation) (12)". ❑

III. INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

The hypothesis that launched the researches in that field was that hyperglycemia associated with insulin resistance is common in critically ill patients, even at those who have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to several complications in such patients, complications that can vary from polyneuropathy and skeletal-muscle wasting to severe infections, sepsis and multiple organs failure and death (13).

Conventional treatment used had as aim to maintain the blood glucose below 215 mg/dl (11.9 mmol/l) using rapid-acting insulin. In the last years, several clinical studies tried to evaluate if a rigorously glycemic control has benefits on different patients populations. One of them is regarding diabetic patients with acute myocardial infarction, at whom therapy to maintain blood glucose at a level below 215 mg per deciliter has shown an improvement in the long-term outcome (14,15,16).

Van den Berghe et al.(17) randomized more 1.500 patients admitted in surgical intensive care units in a clinical study with the aim to compare conventional management of hyperglycemia vs. intensive management for keeping blood sugar levels within tight limits of 80 to 110 mg/dl. The treatment used also rapid-acting insulin, administered continuously intravenous (1UI/1ml), with starting point at a glycemic level of 110mg/dl, also providing proper concomitant nutritional support (enteral feeding is preferred whenever is possible).

This intensive strategy decreased mortality rates from 8.0 to 4.6% ($p<0.04$). Moreover, the intensive treatment was associated with significantly fewer patients staying for >14 days in the ICU, a lower requirement for renal replacement therapy, a lower incidence of hyperbilirubinemia, fewer bloodstream infections, fewer ICU neuropathies, and a reduced need for transfusion and mechanical ventilation. It is questionable if the beneficial results are due to the tight control of blood glucose or to a higher level of circulating insulin. Insulin has other important effects, independent of its effect on glycemia: inhibition of tumor necrosis factor and macrophage inhibitory factor (18,19), prevention of immune system dysfunction (20), modulation of the inflammatory response (21), protection of the endothelium (22), protection of the hepatocyte mitochondrial ultrastructure and function (23) etc.

One of the lacks of this study was that it included patients with moderate disease severity, having a mean APACHE II score of only 9 and a mortality rate of only 8% in the control group. Moreover, almost two thirds of the patients were admitted to the ICU following cardiac surgery.

The main criticisms against this therapeutic strategy regards the increased risk of hypoglycemia (with possible severe outcome for unstable critically patient if remains undiagnosticated) and the higher cost of care (serial blood sugar measurements require additional blood sampling, nursing time, and additional glucose analyzers etc.).

The same group, conducted by van der Berghe, published in 2006 the results of a trial with intensive insulin therapy in a medical ICU, and the results are somewhat different (24). The study included 1200 medical ICU patients who were randomized in two groups: standard therapy vs. intensive insulin therapy and who were predicted to stay for at least 3 days in ICU. Regarding the major outcome of the study (mortality in intensive care) there were no differences between the two groups (26.8% in the conventional treatment group vs. 24.2% in the intensive treatment group, $p=0.30$) but the subgroup analysis shows some interesting results. In the 767 patients group that stayed in ICU at least three days, in hospital mortality was

significantly lower among those who received intensive insulin therapy (43% vs. 52.5%, p=0.009) and also the morbidity was reduced. Surprisingly, among the 433 patients who stayed less than 3 days in ICU, mortality was greater in intensive insulin therapy group. Although the length of stay in the ICU is difficult to predict on admission, these results raised a lot of discussions. The debate is also fired by the results of a German multi-center study of intensive insulin therapy in patients with severe sepsis that was suspended by the safety monitoring board because of a significant excess risk of severe hypoglycemia without any positive effect on mortality (25).

After all these controversial results there are different reactions among the specialists. Some experts consider that we should no more apply intensive insulin therapy until further, larger studies will be developed (26). Others strongly support the intensive insulin therapy for all patients in ICU, associated with clear guidelines for prevention, detection and treatment of hypoglycemia (27).

Waiting for the results of further trials, we consider that in this moment a rational approach is represented by the recommendations of Surviving Sepsis Campaign:

> "Following initial stabilization of patients with severe sepsis, maintain blood glucose <150 mg/dL (8.3 mmol/L). Studies supporting the role of glycemic control have used continuous infusion of insulin and glucose. With this protocol, glucose should be monitored frequently after initiation of the protocol (every 30-60 minutes) and on a regular basis (every 4 hours) once the blood glucose concentration has stabilized (Grade of recommendation D)" (12). ❑

IV. VENTILATION IN ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Respiratory failure is the most common organ failure met at patients in intensive care units. Acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh, who described a syndrome of severe respiratory failure associated with pulmonary infiltrates, similar to infant hyaline membrane disease.(28) The 1994 American-European Consensus Committee defines ARDS as the acute onset of bilateral infiltrates on chest radiography, a partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio of less than 200 mmHg and a pulmonary artery occlusion pressure of less than 18 mmHg, in the absence of clinical evidence of left atrial overload. Among the patients presenting respiratory failure, these ones with acute respiratory distress syndrome (ARDS) have the greatest mortality rate (approximately 40-50%). Some patients have an uncomplicated course and rapid resolution, whereas others may progress to fibrosing alveolitis, which involves the deposition of collagen in alveolar, vascular, and interstitial spaces leading to poor lung compliance. Fibrosing alveolitis has been reported histological as early as 5-7 days. Death usually result from multisystem organ failure rather than lung failure alone (29).

There is a little proof in literature that any therapeutic procedure can reduce mortality among ARDS patients, but mechanical ventilation is mandatory and critical for the survival of these patients (10).

However, inadequate mechanical ventilation may cause additional lung injury, which could aggravate the initial respiratory failure. Ventilator-Induced Lung Injury (VALI) may be caused by over-distention of aerated lung regions, especially when large tidal volumes are used. Ventilator-induced lung injury may also occur if a substantial portion of the lung is not aerated at end-expiration because of atelectasis, flooding, and consolidation. This may cause excessive mechanical forces in aerated lung regions, between aerated and non-aerated lung regions, or in bronchioles and alveoli that open and close with each breath (30).

In a patient with ARDS, regions of the lungs could be so consolidated or atelectatic that it will be impossible to be recruited in order to participate in gas exchange, particularly in dependent regions. The fact that in ARDS only a fraction of the lung really participates in tidal ventilation created the concept of "baby lung", stressing the idea that tidal volumes used for ventilating patients without lung injury (eg., 10 mL/kg) are probably excessive in ARDS and could result in barotrauma, regional overinflation and perpetuation of VALI (31).

The proportion of non-aerated lung may be reduced by applying positive end-expiratory pressure (PEEP). This therapy usually improves arterial oxygenation, but it may cause circulatory

depression and increase pulmonary edema. Moreover, PEEP may increase airway pressures and lung volumes, which could contribute to ventilator-induced lung injury from over-distention.

In 1998, Amato et al. proposed a new approach for improvement of lung function: open lung strategies. This therapeutic approach is based on finding the Pflex (the lower inflection point on the pressure volume curve), and applying a PEEP just above this level, with lower tidal volumes. The mortality was significantly reduced but the technique has many difficulties (Pflex often is impossible to find and over-distension of less diseased tissues may occur) and the optimal setting of positive end-expiratory pressure is still hard to reach (32).

In 2000 an important study was published by the ARDS Network. This multicenter, prospective, randomized trial compared the ventilation with low tidal volumes (6 mL/kg) vs. conventional tidal volumes (12 mL/kg) in patients with ALI/ARDS. Because of the evident positive results (mortality rate 31.0% in low tidal volume group vs 39.8%), the study was stopped early, from ethical reasons, permitting the introduction of the new strategy in the clinical practice (33). This study changed the traditional algorithm of mechanical ventilation into the new one: so called "high frequency/low tidal volumes".

The results of this trial prompted a lot of discussions and the development of further studies. Some authors consider that the results were so impressive because the 12 mL/kg tidal volume is unusual high and a tidal volume of 7-8 mL/kg is equally beneficial as 6mL/kg (10).

Another important debate was created by the search of the ideal level of PEEP and the possible beneficial role of high-PEEP levels. In 2004, the results of ALVEOLI study (549 patients) showed that in patients with acute lung injury and ARDS who receive mechanical ventilation with a tidal-volume goal of 6 ml per kilogram of predicted body weight and an end-inspiratory plateau-pressure limit of 30 cm of water, clinical outcomes are similar whether lower or higher PEEP levels are used (34).

The "recruitment maneuver", utilizing a continuous positive airway pressure (CPAP) of 35 to 40 cmH20 for 40 seconds or a so called "sigh" breathing with a high tidal volume prior to reinstitution of the previous level of PEEP should be considered in patients with ARDS after temporary disconnection from ventilator (eg., for suctioning or nursing). This may be an useful intervention because there are data showing that a single breath without PEEP could result in compressive atelectasis and alveolar derecruitment (35).

Fortunately, the risk of significant lung over-distention do not appear to occur secondary to a recruitment maneuver (36). At present, there is no consensus to support the routine use of recruitment maneuvers in patients with ARDS but sigh breaths can be used to overcome derecruitment following disconnection from the ventilator (37).

Although the debate continues around the subject of ventilation in ALI/ARDS, we will conclude this chapter with the recommendations of the Surviving Sepsis Campaign regarding sepsis-induced ALI/ARDS (12):

1. Avoid high tidal volumes and high plateau pressures. The goals to be obtained in 1-2 hours interval are a low tidal volume (6 mL/kg) and an inspiratory plateau pressure <30 cm H20- recommendation grade B.
2. Permissive hypercapnia can be tolerated if required to minimize plateau pressures and tidal volumes – recommendation grade C.
3. PEEP values according with the severity of oxygenation deficit and the values of FiO2 are recommended – grade E. The oxygenation goal is to reach a PaO2 between 55-80 mmHg or SpO2 88-95%. For achieving this goal incremental FiO2/PEEP combinations should be used (starting from 0.3/5cmH2O until 1.0/24 cmH2O), with high respiratory rate (maximum 35 breaths/min) and plateau pressure below 30 cm H2O.
4. Prone position should be considered if the oxygenation is difficult, requiring high levels of FiO2 and plateau pressures – recommendation grade E.
5. Semi recumbent position, with the head at 45° it is recommended, if there are no contraindications, in order to prevent ventilator-associated pneumonia – recommendation grade C.
6. A weaning protocol, based on a spontaneous breathing trial in order to evaluate the ability to discontinue the mechanical ventilation is recommended – grade A. ❑

V. RENAL REPLACEMENT THERAPIES IN CRITICALLY ILL PATIENTS

The acute renal failure remains an unsolved problem in intensive care medicine, despite the availability of renal-replacement therapies. Acute renal failure (due to acute tubular necrosis in most of cases) causes a high mortality rate among critically ill patients, independent from other associated pathology. Different regimens of therapies were assessed in order to establish the most beneficial in intensive care units, due to particular status of critically ill patients. Many of patients can have pre-existing conditions that predispose them to acute renal failure (ARF) and to concomitant extra-renal complications that can cause multi-organ failure (38,39). ARF and its associated metabolic alterations also appear to increase the risk of severe extra-renal complications, which are often fatal for patients admitted in intensive care units (40,41).

In a study published in 2002, Schiffl et al. have demonstrated that a regime of daily hemodialysis (DH) was superior to alternate-day hemodialysis (ADH) in this population of patients who typically have a high mortality. Also, in the group that received as treatment for acute renal failure the daily hemodialysis, were noted a better uremic control, fewer hypotensive episodes, and more rapid resolution of that organ failure. Notably, among those patients with a normal urinary output at enrolment, 73% in the ADH group and only 21% in the DH group became oliguric. This could be related to the fewer hypotensive episodes in the DH group. Better uremic control and improved volume status could have contributed to the improved survival as well (42).

This study, correlated with another study published by Ronco et al.(43), sustain the use of renal replacement therapy in the form of DH or continuous veno-venous hemofiltration in all patients in the ICU with ARF.

These 2 modalities of renal replacement therapies (intermittent daily hemodialysis – IDH and continuous veno-venous hemofiltration – CVVH) are used without knowing which is the best for critically ill patients or if one of them is better tolerated by a particular subgroup of patients.

It was thought that CVVH may be more effective than IDH in the treatment of critically ill patients that are hypotensive but, for a long period, studies comparing these 2 modalities have been of poor quality except a small trial in which the differences between the two techniques were not significant (44).

This was the point for starting the HEMODIAFE study that aimed to compare CRRT with IDH in this class of critically ill patients, starting from the hypothesis that CVVD is safer and superior to IHD in terms of survival and adverse events (45).

The HEMODIAFE study is a multicenter randomized clinical trial, and enrolled 184 patients to IDH and 175 patients to continuous veno-venous hemo-diafiltration (CVVHDF). There were no significant differences between the two groups regarding the demographic data and the severity of renal dysfunction but the patients in the IDH group were more septic (68.9% vs. 56%, $P = 0.01$). The majority of patients (>85%) needed vasopressor support and almost all (> 94%) presented respiratory failure imposing mechanical ventilation.

There were no significant differences between the 2 groups regarding the overall ICU and in-hospital mortality rates (66% and 72%, respectively), 60-day survival rates (32.6% in CVVHDF group vs. 31.5% in IDH group, $p = 0.98$), hypotensive episodes (35.4% vs. 39.1%, $p = 0.47$), bleeding, ICU and in-hospital LOS, or thrombocytopenia. CRRT resulted in less hemodynamic alterations and allowed better volume, uremic, and nutritional control. In addition, CRRT was more efficient in the removal of middle-sized molecules. On the other hand, because the patients in IHD group were more septic but there were no differences between groups in mortality, it is reasonable to appreciate that IHD was more effective in sepsis associated with acute renal failure.

In conclusion, both methods are safe and effective in critically ill patients with acute renal failure and are considered equivalent, with a grade B of recommendation (12). It remains the question if a particular subgroup of patients will actually benefit from one of these two therapies, but the answer can be obtained only by accumulating a large number of heterogeneous patients in further studies. ❑

VI. USAGE OF STEROIDS IN SEPTIC SHOCK

Sepsis is an inflammatory disease and for a long period of time the high dose corticoids was considered a logical therapeutic approach, but in two randomized, prospective clinical trials and two meta-analyses the results were quite opposite, indicating that high-dose corticoids are not only ineffective but can have a deleterious effect (46,47,48). These results seemed to be the end for steroids in sepsis but a few studies have indicated that at least a part of patients in septic shock may have a relative adrenal insufficiency, defined as a moderate increase (9μg mL) in cortisol after a stimulating dose of adrenocorticotropic hormone (ACTH) and therefore may benefit from moderate doses of hydrocortisone (49). This hypothesis has been confirmed by the multicenter, randomized, controlled trial conducted by Annane that has shown an increased mortality in patients in septic shock with adrenal insufficiency compared with those with normal adrenal function and the fact that the treatment with hydrocortisone reduced mortality in a significant manner (50). The results were confirmed by other studies (51,52) and the use of hydrocortisone, 200-300 mg per day, in three or four divided doses or by continuous infusion, for a period of 7 days, was introduced in the guidelines of Surviving Sepsis Campaign for the treatment of septic shock (grade C of recommendation) (12).

Some experts consider that the hydrocortisone should be stopped after the resolution of shock (53) and others recommend the tapering of the dose at the end of therapy (54) (grade E of recommendation). With the same grade of recommendation, some would add also fludrocortisone 50 μg orally four times per day to hydrocortisone (50).

Despite the differences regarding the administration of moderate doses of steroids, there is a consensus that doses of hydrocortisone greater than 300 mg per day should not be used in patients with septic shock (grade A of recommendation). However, if the patient is on a chronic steroid therapy, he will continue this and if the medical condition imposes a stress dose could be used (12). ❑

VII. THE USE OF DROTRECOGIN ALFA (ACTIVATED) IN SEVERE SEPSIS/SEPTIC SHOCK

Severe sepsis represents a major problem in hospitals and intensive care units worldwide, because it's high mortality rate. Activated recombinant protein C (drotrecogin alfa) (rhAPC) became a standard component of many treatment algorithms after it was shown to have a beneficial effect on mortality vs. placebo in the PROWESS trial (55). The indication was based on the fact that the inflammatory response in severe sepsis is integrally linked to pro-coagulant activity and endothelial activation. The inflammatory response in sepsis is pro-coagulant in the early stages, and drotrecogin alpha is an endogenous anticoagulant with anti-inflammatory properties. The PROWESS study has shown that drotrecogin alpha significantly improved survival in adults with severe sepsis, with a 29% reduction in relative risk of death in the group that received active drug compared with placebo. The trial was halted early because of the strong positive result and the FDA granted approval of Xigris® for this indication in November 2001. The mode of action of drotrecogin alpha is very complex and has not been entirely elucidated. The anticoagulant effect can not explain alone the impact in severe sepsis, two other natural anticoagulants, antithrombin and tissue factor pathway inhibitor showing negative results in well designed studies (56,57). It is now clear that rhAPC is unique in the fact that combines the modulatory effect on the inflammatory system with an anticoagulant one, and other ongoing studies suggest that this drug has also anti-apoptotic protective effects on endothelial cells (58,59).

Surviving Sepsis Campaign guidelines stipulated that drotrecogin alpha is recommended in severe sepsis patients at high risk of death (with APACHE II score > 25), when there is no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit of this drug, with a grade B of recommendation (12).

Standard treatment includes doses of 24 micrograms/kg bodyweight/hour, administered continuous intravenously for 96 hours. The dose should be interrupted in case of performing invasive parenteral procedures (1 hour before and 1 hour after procedure) or surgical interventions (1 hour before and 12 hours after intervention). At present, risk assessment is best determined by bedside clinical evaluation and judgment. Because of the uncertainty of risk assessment and the potential for rapid deterio-

ration of patients with severe sepsis and septic shock, when a patient has been identified as at high risk of death, treatment should begin as soon as possible (55).

The most important risk associated with the use of rhAPC is bleeding, although it is clear that the benefit outweights the risk.

Moreover, the results of two large studies, including together of more than 2.600 patients, (ENHANCE and ENHANCE US trials, presented in 2003 and 2004), support the beneficial effects of drotrecogin alpha on outcome, also showing a good safety profile. The global mortality rate in these single-arm prospective studies was with 6% lower than in the placebo group from PROWESS trial, and severe adverse events occurred in 4% of cases, comparative with 2.8% in PROWESS placebo group (60,61).

The ADRESS study evaluated the efficacy and safety of this drug in adult patients with severe sepsis who were determined to be at low risk of death (APACHE score less than 25) (62). The ADDRESS trial enrolled patients older than 18 years with recent onset of severe sepsis, comparing drotrecogin alpha with placebo. There were no differences between drotrecogin and placebo groups, regarding 28-day or in-hospital mortality (28-day mortality 18.5% vs. 17%; $p = 0.38$), in-hospital mortality (20.6% vs. 20.5%; p = NS). Although the study was designed for the enrolment of 11,000 patients, enrolment was stopped after randomization of 2640 patients due to a low likelihood to demonstrate significant differences and benefit to low-risk patients. The effect of these results is that drotrecogin alpha is no more indicated in septic patients with an APACHE II score of < 25 or presenting a single organ dysfunction (10).

Children represent another subgroup of septic patients who may benefit from this drug. But the results of RESOLVE trial, published in January 2006, 63 were that drotrecogin alfa has no effect on reducing severe sepsis in children and increases the incidence of central nervous system (CNS) bleeding in infants. The trial has been halted early due to non-futility. RESOLVE trial tested the efficacy of drotrecogin alpha in a paediatric population with severe sepsis. This international trial involved 477 children randomized to either active drug or placebo. The incidence of serious adverse events was similar during drug infusion in the two arms of the trial (occurring in 10.4% of children on drotrecogin alpha and 11% on placebo). During 28 days of follow-up, the incidence was 18.3% in the study group and 19.0% in placebo patients. Bleeding events were also similar in the two groups during infusion and follow-up, at 3.8% and 3.4% for drotrecogin alpha and placebo, respectively, during infusion, and 6.7% and 6.8%, respectively, during follow-up, but the incidence of central nervous bleeding was higher with drotrecogin alpha at 2.1% versus 0.4% with placebo. The higher incidence of CNS bleeding was confined to children less than two months of age.

The major finding was that the efficacy of the drug was no higher than that of placebo in children with severe sepsis. Twenty-eight-day all-cause mortality was 17.45% in placebo patients and 17.15% in the study group. The trial was not powered to completely evaluate efficacy. There is some indication that drotrecogin alpha confers benefit in the subgroup of children with disseminated intravascular coagulopathy (DIC).

After the results of this study were published, Xigris® (drotrecogin alpha) labelling has been changed from indicating that the safety and efficacy of the drug had not been evaluated in children to stating that Xigris® is contraindicated for paediatric use. ❑

VIII. CONCLUSION

Despite all the controversies, we live in an era of Evidence-Based Medicine, that proved to be the best approach in order to optimize the medical act, to concentrate in practical recommendations, guidelines and protocols the vast experience offered by specific tools like Randomized Clinical Trials, meta-analyses, consensus meetings, expert opinions etc.

But creating guidelines is only one step, that needs to be followed by the implementation in the clinical practice, and there are data suggesting that there are a lot to do in this field.

Evidence-Based Medicine penetrated difficult in the complex environment of ICU, were the heterogeneity of patients and the diversity of therapeutically and monitoring methods made difficult to evaluate the impact of a specific factor or treatment on outcome. The last years imposed however a few therapies – a part of them presented in our review – with a proven, major impact in the outcome of critically ill patients.

At the end, we have to say that the guidelines and protocols that concentrate the results of EBM should not be seen as static documents, but rather as a dynamic process, that need to continuously adapt to the new evidences, in order to improve the outcome of our patients. ❑

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