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REVIEW ARTICLE

Adrenal insufficiency in children with septic shock

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Abstract

Objective: To review the criteria for diagnosing and treating adrenal insufficiency in patients with septic shock.

Sources of data: Articles published in Brazilian and foreign journals selected through these publications' websites and Medline, as well as references cited in key articles

Summary of the findings: The literature reports a range betwen 17 and 54 % for the finding of adrenal insufficiency in patients with septic shock. There is no consensus for diagnosing adrenal insufficiency in patients suffering from critical diseases, particularly in patients with septic shock. The presence of volume-refractory and catecholamine-resistant septic shock suggests this condition, while basal cortisol under 25 µg/dl is a diagnostic criterion indicating adrenal insufficiency. The adrenal stimulation test is a useful resource for identifying patients with relative adrenal insufficiency. Our testing option for adrenal stimulation in children is the use of corticotropin in low doses (0.5 µg/1,73 m²). An increase of less than 9 µg/dl in the value of postcorticotropin-stimulated cortisol suggests the presence of occult (relative) adrenal insufficiency. In patients with septic shock presenting adrenal insufficiency, either suspected or confirmed, the administration of hydrocortisone in shock or stress doses can be vital for a favorable clinical outcome.

Conclusions: The existing data, although controversial, already provides a basis to determine when to begin hormone replacement therapy, the serum level of cortisol accepted as adequate, and the choice of corticotropin doses for performing the adrenal stimulation test and diagnosing occult or relative adrenal insufficiency in patients with septic shock.

J Pediatr (Rio J) 2003;79(Suppl 2):S169-S76: Sepsis, septic shock, adrenal cortex, adrenal gland hypofunction, glucocorticoids, adrenal cortex function tests.

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Introduction

The functions of the endocrine system are often altered in individuals with a wide range of acute diseases, and this is what generally occurs with glucocorticoid secretion. The secretion of cortisol often presents elevated levels in acute diseases such as myocardial infarction, infection, and with patients subjected to surgical procedures and also in situations where there is shock.[1]

The alterations to adrenal function among critically ill individuals, especially those with septic shock deserves highlighting.[1] A number of different studies, the majority of adults, have tried to relate adrenal function to the evolution of these patients. The greater part of the divergence among published studies relates to the criteria used to define the presence of adrenal insufficiency, and also of the so-called occult adrenal insufficiency.

The importance of these definitions gains prominence to the extent that the controversy resurfaces over whether or not to use corticosteroids with critically ill patients, particularly when they present altered hemodynamic states. More specifically, with septic shock patients, the use of corticosteroids has passed through various stages. During the seventies and until the last few years of the eighties the administration of high doses of intravenous corticosteroids was common in the treatment of sepsis and septic shock based on research which showed positive effects.[2] Later, other studies provided evidence that the use of corticosteroids produced no change to mortality or could even increase it as a result of secondary infections, with the result that it was no longer routinely used.[3-6] Recently, new work has been published on this group of septic shock patients, some of which has demonstrated better evolution when corticosteroids were used, principally in a group of patients dependent on the use of catecholamines for hemodynamic equilibrium maintenance.[7-11]

Recently, a number of different studies have evaluated adrenal gland function in critical patients with sepsis and septic shock, attempting to establish a relationship between adrenal response considered insufficient for the moment with the intensity of hemodynamic alterations and also its repercussion on treatment and evolution. These studies have found an incidence of insufficient renal function of from 17% to 54% and some of them established an association with the severity of the disease.[12-19]

In 2002, the American Institute of Medicine requested the development of directives and clinical practice parameters for the hemodynamic support of newborns and children in septic shock in an attempt to, once implemented, improve the outcome of these patients. Specialists affiliated to the Society of Critical Care Medicine, evaluated the literature, selected specific recommendations and reviewed the compiled recommendations. The president of this task force continuously compiled and modified the document until less than 10% of the specialists disagreed with the recommendations. The task-force agreed that adrenal insufficiency and, in particular, a hypoaldosteronist state may be more common than was thought and that replacement with hydrocortisone could save the lives of children with septic shock resistant to the use of catecholamines. Finally, the consensus of this committee recommends the use of hydrocortisone, and not methylprednisolone, strictly for children with shock that resists catecholamines and with a suspicion or confirmation of adrenal insufficiency. This committee also opted for more conservative diagnostic criteria for adrenal insufficiency, defining it as total cortisol less than or equal to 18 µg/dl.[20]

Therefore, it is believed that if there is any benefit in the use of corticosteroids, then this should be related to the group of patients who present inadequate renal function. Thus, for more rational replacement of the substance it becomes necessary to define which patients present adrenal response below that to be expected for the acute point of their condition. The objective of this review is to find within work in published literature the criteria used by the different researchers to evaluate adrenal function, performing a critical analysis of these criteria, as we believe that acute adrenal insufficiency is a common and little diagnosed condition among critically ill patients.

The hypothalamus pituitary adrenal axis and cortisol secretion

The secretion of cortisol is controlled by the hypothalamus-pituitary-adrenal axisand generally follows a circadian pattern, with the highest concentrations being observed in the morning. Thus, the concentration of cortisol at 8 o'clock in the morning reflects the endogenous activity of the hypothalamus-pituitary-adrenal axis.[21] A number of different neurological or hormonal stimuli are received by the central nervous system and transmitted to the hypothalamus with, consequentially, increases or decreases secretion of the hormone and liberation of corticotropin-releasing hormone (CRH). The CRH hormone, on reaching the anterior pituitary stimulates the liberation of corticotropin, also known as the adrenocorticorticitropic hormone (ACTH), which will stimulate the adrenal gland to liberate glucocorticoids which, in turn, will act on the hypothalamus-pituitary-adrenal axis establishing a negative feedback mechanisms, with a resultant reduction in the liberation of CRH and ACTH. A range of substances (cytokines, endogenous peptides and other hormones) and situations (pain, tissue damage, surgery, hypoxemia, hypotension, hypoglycemia) modulate the h, resulting in a system which can respond in situations of stress with minute by minute changes to cortisol liberation.[15]

In serious cases, as stated above, an increase in serum cortisol levels is to be expected, particularly when there is sepsis and septic shock.[13,22] Specifically with these patients this response is not only due to physical stress, but also to the liberation of cytokines into the plasma, by immune cells, during the inflammatory process.[15] The three main cytokines involved are tumor necrosis factor a, interleukin-1 and interleukin-6, contribute significantly to stimulate the hypothalamus-pituitary-adrenal axis, both synergistically and independently.[23] On the other hand, with critically ill individuals, adrenal insufficiency may occur as a result of hypothalamus-pituitary-adrenal axisexhaustion, exhaustion of the adrenal cortex (lack of adrenal reserves), reduced cortisol production capacity and, with children, due to immaturity of the axis. When adrenal insufficiency occurs

during septic shock it is transitory and normal function is reestablished when the individual recovers. While cytokines have a role in stimulating the axis, they may also be related to glandular dysfunction in these patients. Tumor necrosis factor a, for example, despite potently inducing the secretion of adrenocorticotrophic hormone, inhibits adrenal function by impeding the action of this hormone, thus reducing cortisol synthesis.[15]

The greatest controversy has been over what level of cortisol represents an acceptable adrenal response to stress, and below which value a patient should be considered as and treated like a patient with adrenal insufficiency. Drucker and Shandling,[1] in 1985, studying 40 patients admitted for clinical diseases at an intensive care unit, found an average baseline serum cortisol level of 45 µg/dl (1232 nmol/l). Bone et al.,[18] in work published in 2002, in which they studied 65 children with meningococcal disease, found an average cortisol level at admission of 41.5 µg/dl (1122 nmol/l). Rivers et al.[24] evaluated adrenal function in 104 patients submitted for surgery who required vasopressors and found an average baseline cortisol of 29.9 µg/dl. In this study, a group of patients treated with corticosteroid presented a good response with withdrawal of the vasopressors in 24 hours. The average baseline cortisol for this group was 20 µg/dl and only one individual had a level above 25 µg/dl. In the group of patients who did not respond to corticosteroid treatment, the value for baseline cortisol was 49 µg/dl and only two presented baseline cortisol below 25 µg/dl. This study by Rivers suggests that baseline cortisol below 25 µg/dl is associated with hypotension that is responsive to treatment with corticosteroids. Shein et al.,[25] studying 37 patients with septic shock, found an average baseline cortisol level of 50.7 µg/dl and only 8% of them presented a value below 25 µg/dl.

Criteria used to define adrenal insufficiency

The authors used varying criteria to define the presence of adrenal insufficiency in critical patients, making interpretation of their results confused and giving rise to heated discussion. The incidence of adrenal insufficiency reported in literature for patients in septic shock, suffers from a strong influence from the criteria adopted to define the diagnosis oscillating from 17% to 54%.[12,14,16,18,19,22]

With respect of adults work proliferates on adrenal insufficiency in severe cases, particularly sepsis patients. Work by Annane et al.[12] performed at an intensive care unit in France merits prominence as does work by Marik and Zaloga[26] carried out in Washington. The work by Annane et al.[12] was to study, in individuals with septic shock, the prognostic value of baseline cortisol levels (T0), collected immediately before a test with synthetic ACTH and of the response of cortisol to this test, i.e. maximum variation (Δmax) between cortisol post-test and baseline. Annane[12] evaluated mortality in terms of T0 < or > 34 µg/dl, Δmax < or > 9 µg/dl and in relation to the following combinations of T0 and Δmax: I) T0 < 34 mg/dl and Δmax > 9 µg/dl; II) T0 < 34 µg/dl and Δmax < 9 µg/dl; III) T0 > 34 µg/dl and Δmax < 9 µg/dl. Death occurred more rapidly among individuals with T0 > 34 µg/dl (average time of 6 days), in those with Δmax < 9 µg/dl (average time of 11 days), and with the combination of T0 > 34 µg/dl and Δmax < 9 µg/dl (average time 5 days). In the combined analysis (T0 and Δmax), based on the 28th day of the study, group I (T0 < 34 µg/dl and Δmax > 9 µg/dl) presented the best prognosis with a mortality rate of 28%, group II (T0 < 34 µg/dl and Δmax < 9 µg/dl) was in the intermediate position with a mortality rate of 67% and group III (T0 > 34 µg/dl and Δmax < 9 µg/dl) had the worst prognosis with a mortality rate of 82%. The incidence of relative adrenal insufficiency (occult), accepting the criteria defined by the author, a cortisol response to testing with 250 µg of synthetic ACTH of less than 9 µg/dl, was 54%. Furthermore, the presence of occult adrenal insufficiency, as often as not identified in association with baseline cortisol levels above 34 µg/dl, had a relationship with higher mortality levels in the group of patients studied. Marik and Zaloga[26] however, took as their objective to determine what the best method was for discriminating adrenal insufficiency with 59 patients in septic shock and, to achieve this, evaluated as indicators, baseline cortisol less than 25 µg/dl, the response to testing with synthetic ACTH in low doses (1 µg) and the response to testing with synthetic ACTH in high doses (250 µg). These indicators were evaluated in relation to the outcome of the withdrawal of vasoactive drugs in up to 24 hours after the introduction of treatment with hydrocortisone. The group of patients that responded to corticoids presented a baseline cortisol of 14.1 + 5,2 µg/dl, whereas the unresponsive group presented baseline cortisol at 33.3 + 18 µg/dl. Within the group of individuals that responded to therapy with hydrocortisone, 95% presented a baseline cortisol below 25 µg/dl, although, while 54% were diagnosed as having adrenal insufficiency by the low dose ACTH test, only 22% were picked up by the high dose test. The specificity of these indicators was 57%, 97% and 100%, respectively. The area beneath the Receiver Operating Characteristic Curve, (ROC), for baseline cortisol at 25 µg/dl was 0.84. The best point for adrenal insufficiency identification, taking into account the response to steroid treatment, was a baseline cortisol concentration of 23.7 mg/dl giving a sensitivity of 0.86; a specificity of 0.66; a likelihood ratio of 2.6; a positive predictive power of 0.62 negative predictive power of 0.88.

When it comes to the pediatric age group the difficulties are even greater as a result of the small number of recent publications and the varying criteria used for diagnosis depending on author. In this age group work by Hatheril et al.,[16] Menon and Clarson,[19] Bone et al.,[18] and Pizarro[27] deserve prominence - the last carried out in Brazil (Table 1).

The study by Hatheril et al.[16] was performed with children with an average age of 48 months (varying from 01 to 192) and with a diagnosis of septic shock. For this study the primary criteria for a diagnosis of supra-renal insufficiency was defined as increased serum cortisol in relation to the baseline, after stimulation with a 145 µg/m² dose of synthetic ACTH. A rise from the base cortisol level of less than 7 µg/dl (200 nmol/l) was considered as supra-renal insufficiency and by this criteria, a supra-renal insufficiency incidence of 52% was obtained. If other criteria had been used the incidence, with the same group of patients, would have varied from 12% to 85%. On the other hand, Menon and Clarson[19] defined supra-renal insufficiency as the presence of laboratory results for the cortisol base value of less than 7 µg/dl, or a peak cortisol value after synthetic ACTH stimulation of less than 18 µg/dl, or both. These authors used a 125 µg dose of synthetic ACTH in children weighing less than 10 kg and 250 µg in children over 10 kg and by these criteria found an incidence of supra-renal insufficiency of 31%. Menon and Clarson[19] also compared their findings with other criteria defined in literature supra-renal insufficiency diagnosis finding a variation of between 8% and 31% depending upon the criteria adopted. Bone et al.[18] evaluated the hypothalamus-pituitary-adrenal axisin children aged between 0.2 and 15 years with diagnoses of meningococcal disease. The criteria these authors used to define adrenal insufficiency were a morning base cortisol value of less than 5 µg/dl (140 nmol/l) or a peak cortisol value of less than 18 µg/dl (500 nmol/l), after adrenal stimulation with a 0.5 µg/m² (500 ng/m²) dose of synthetic ACTH. Of the 65 patients studied and by the criteria employed 17% presented adrenal insufficiency and morning base cortisol level, when a cut-off of 14.5 µg/dl (400 nmol/l) was used, returned a sensitivity of 83% and a specificity of 81% when compared with cortisol after testing with synthetic ACTH. Finally, Pizzaro et al.[27] studied 48 children with severe sepsis or septic shock. In this study, adrenal insufficiency was defined as the presence of base cortisol values below 20 µg/dl associated with an increase less than or equal 9 µg/dl after adrenal stimulation testing with 250 µg corticotropin and relative adrenal insufficiency as base cortisol equal to or greater than 20 µg/dl but with an increase after stimulation less than or equal to 9 µg/dl. The incidence of adrenal insufficiency encountered was 17% and relative adrenal insufficiency was 25%.

Adrenal function testing

Many tests are used to evaluate the function of the hypothalamus-pituitary-adrenal axis, but none of them has a greater capacity than endogenous stress situations (hypotension, hypoglycemia, hypoxemia) which evaluate the axis in its entirety. The insulin tolerance test, the metapyrone test, the standard corticotropin stimulation test and the low dose corticotropin test have all been used.[21,28]

The insulin tolerance test is considered by many to be the most valuable test for determining adrenal insufficiency. This test provokes hypoglycemia stimulating the hypothalamus and the pituitary to liberate ACTH making it possible to evaluate the entire axis. However, in addition to being uncomfortable for the patient, the test can be the cause of innumerable complications, including adrenergic and neuroglycopenic symptoms, and is contra-indicated for individuals with cardiovascular disease, the aged and when there is a history of convulsions.[21,29]

Table 1 - Incidence of adrenal insufficiency, diagnostic criteria and dose of ACTH used for adrenal stimulation in the studies on adrenal insufficiency in children with septic shock

Authors	Diagnostic criteria Cortisol (µg/dl)	Dose of ACTH used for adrenal stimulation	Results (%)
Hatheril[16]	Increase after ACTH < 7	145 µg/m²	52
Menon[19]	Basal cortisol < 7 Cortisol peak after ACTH < 18	Weight < 10 kg: 125 µg Weight > 10 kg: 250 µg	31
Bone[18]	Morning basal cortisol < 5 Cortisol peak after ACTH < 18	0.5 µg/m²	17
Pizzaro[27]	Basal cortisol < 20 + increase of cortisol after ACTH ≤ 9	250 µg	17

ACTH: adrenocorticorticitropic hormone, kg: kilogram, %: per cent, µg: microgram, m²: square meter.

The metapyrone test was developed specifically to evaluate adrenal function and is perhaps most sensitive for this purpose. Metapyrone acts to inhibit the adrenal enzyme 11ß- hydroxylase, which converts 11-deoxycortisol to cortisol in the final stage of steroidogenesis. The 11-deoxycortisol, not having glucocorticoid effects, does not inhibit the production of ACTH. The administration of metapyrone to a normal individual after causing a reduction in serum cortisol stimulates ACTH production resulting in an accumulation of 11-deoxycortisol, which does not occur in individuals with adrenal insufficiency. When adrenal function is adequate, the serum level of 11-deoxycortisol is above 7 µg/dl, whereas values below 7 µg/dl associated with reduced serum cortisol give a diagnosis of adrenal insufficiency. The length of time required for its completion, at least 8 hours between administering metapyrone and the serum assays, as well as the possibility of the results being affected by the use of other drugs: glucocorticoids; phenytoin; and phenobarbital and the reduction of serum cortisol caused by the test itself make it of little use in severe cases, particularly those where there is sepsis which appears to worsen in the presence of reduced cortisol levels.[29]

For patients with acute diseases, particularly those with sepsis and septic shock preference had been given to testing with corticotropin. A significant proportion of researchers preferred a 250 µg dose of this hormone, which is considered the standard test. Using this test dosage has been demonstrated to result in some patients who had been classed as having adequate adrenal response will later be diagnosed as having adrenal insufficiency. In virtue of this fact, a group of researchers, also significant, used a significantly smaller dose of ACTH, 0.5 to 2 µg, to stimulate the adrenal gland. Another large variation was in terms of the manner in which these doses are employed; while some used fixed doses others related them to body surface area.

In pediatrics, authors prefer to use the standard test (high dosage) and have also used variable doses: Hatheril et al.[16] used 145 µg/m², Menon and Clarson[19] fixed doses of 125 µg for children less than 10 kg and 250 µg for children above this weight. Bone et al.[18] opted to test with low dosages and used 0.5 µg (500 ng) of 1-24 corticotropin/m².

The popularity of the synthetic ACTH test to evaluate hypothalamus-pituitary adrenal axis function is due to the simplicity and speed with which it can be performed. The other tests, as has been described, while offering more trustworthy results are more difficult to carry out and are contra-indicated for some patients.

The standard synthetic ACTH test is performed with the administration of 250 µg of intravenous or intramuscular synthetic ACTH associated with serum cortisol level measurement immediately before administration and 30 and 60 minutes afterwards. More recently, beginning in the nineties, some researchers have defended the use of a smaller dose (1 µg) of ACTH. Dickstein et al.,[30] in 1991, analyzed the cortisol response to stimulation with 250, 5 and 1 µg doses of ACTH. In healthy individuals serum cortisol assayed at 30 minutes was similar irrespective of the ACTH dose used, while in six chronic steroid using patients the serum cortisol results were considered normal with a 250 µg dose of ACTH, but in five out of six was considered below normal when a 1 µg ACTH dose was used for stimulation. Tordjman et al.,[31] in 1995, compared the use of ACTH with metapyrone and insulin tolerance tests, with healthy individuals and with proven alterations to the hypothalamus-pituitary-adrenal axis. In this study all of the individuals with adrenal insufficiency were identified by serum cortisol assay 30 minutes after a 1 µg dose of ACTH. However, 70% of the patients with adrenal insufficiency were not identified when the dosage was 250 µg or 5 µg. Tordjman et al.,[32] in 2000, evaluated the performance of the synthetic ACTH test, at doses of 250 µg and 1 µg, as a screening technique for hypothalamus-pituitary-adrenal axisfailure. This study, which used a post-test cortisol level of 18 µg/dl (500 nmol/l) as the cut off for adequate adrenal response was carried out with three groups of individuals: healthy; pituitary disease with normal axis function; pituitary disease with axis failure. The adrenal stimulation test with 1 µg of ACTH identified 18 of the 19 individuals with altered axis function, presenting a sensitivity of 94.7% and a likelihood ratio of 0.0588 of a negative result. In contrast, the test with 250 µg of ACTH presented, for the same group, a sensitivity of only 6.2% and a likelihood ratio of 0.875 for a negative test, failing to identify 15 of the 16 individuals who also had this test performed. Furthermore, the test with 1 µg of ACTH returned a result of adequate response for all of the healthy individuals and for 36 of the 43 in the group with pituitary disease but with axis function considered normal by other tests, presenting a specificity of 90 %.

Equally important is work done by Crowley et al.[33,34] published in 1991 and 1993 which compares the standard 250 µg/1.73 m² ACTH dose with an even smaller dose of just 0.5 µg/1.73 m². These studies demonstrated that this low dosage was sufficient to provoke maximum adrenal stimulation in all participants and that the magnitude of the increase in cortisol over the first 20 minutes was identical with either dosage although there were significant differences between them at 30 minutes. With the 250 µg/1.73 m² dose the serum cortisol concentration increased until 75 minutes whereas it began to fall by 30 minutes when the 0.5 µg/1.73 m² dose was used. These results are similar to those found by Dickstein et al.[30] which confirmed the capacity of a 1 µg dose of ACTH to provoke maximum cortisol response 30 minutes after its administration.

Still on the subject of ACTH stimulation tests, two articles deserve citation for having studied individuals within the pediatric age range: Broide et al.[35] and Agwu et al.[21] Broide et al.[35] used a 0.5 µg/1.73 m² dose of ACTH and compared it with a standard 250 µg/1.73 m² dose for the diagnosis of mild adrenal insufficiency in asthmatics, the majority of whom were children (30 out of 46), using inhaled corticosteroids and concluded that the low ACTH dose adrenal stimulation test presented a greater capacity to

identify patients with mild adrenal insufficiency. Agwu et al.[21] performed a study of 32 individuals aged between 2 and19 years with suspicion of adrenal insufficiency. The author used the test at ACTH dosages of 250 µg/1.73 m² and 0.5 µg/1.73 m² and measured the cortisol response at 30 minutes. The diagnosis of adrenal insufficiency was defined as a post-test cortisol level below 18 µg/dl (500 nmol/l) or an increase of less than 7 µg/dl (200 nmol/l) compared to the level before ACTH administration. Of the 32 patients who were evaluated, 21 presented an acceptable cortisol response and three an abnormal response with both tests, whereas eight patients presented a response considered acceptable with the high dose, but an inadequate response with the 0.5 µg/1.73 m² dose. This study was limited by the fact that it did not compare the results with a more trustworthy test such as the insulin tolerance test, as there was a possibility that adrenal insufficiency had been over diagnosed. This comparison, however, was performed by Rasmussen et al.,[36] who demonstrated a greater correlation between the 1 µg ACTH test and the insulin tolerance test than is obtained with the standard 250 µg ACTH test. Furthermore, the 250 µg ACTH test can cause a blood concentration of the hormone of up to 60,000 pg/ml, whereas with the lower doses (0.5 and 1 µg) the concentration remains at around 100 pg/ml, similar to the concentrations that occur during stress situations which vary between 40 and 200 pg/ml.[26]

Certain studies have questioned this greater capacity of the low dose ACTH tests to diagnose adrenal insufficiency. This class includes work by Mayenchnecht et al., but even this confirms that low dose tests produce a similar response to that obtained with the test that is considered standard.[37]

In an interesting evaluation of the available adrenal insufficiency diagnostic tests, Thaler and Blevins,[38] analyzed a number of different articles in an attempt to establish the likelihood ratio, sensitivity and specificity of these tests. The likelihood ratio is the ratio between the probability of a given result for a test when performed on unwell subjects and the probability of the same result occurring when the test is applied to a healthy subject. In the case of adrenal insufficiency the likelihood ratio indicates how many times more likely a given test result is to occur with individuals with adrenal insufficiency than with individuals without this diagnosis. The results of this study demonstrate that the 1 µg dose of ACTH is extremely sensitive (94% to 100%), specific (88% to 100%) and presents a likelihood ratio which defines significant changes from pre-test to post-test probability. Compared to the test with 250 µg of ACTH, the 1 µg test presents a lower negative result probability ratio (0 to 0.06), giving greater confidence in the adrenal gland's capacity to produce corticosteroids when the test result is normal.

Sepsis and the circadian rhythm

A number of different stimuli (pain, hypovolemia, hypotension, tissue damage) result in a persistent increase in the ACTH hormone and of cortisol secretion leading to loss of the daily variations in hormone levels. This loss of circadian rhythm in critically ill patients or those subjected to surgical procedures has been demonstrated in a number of different studies. With such patients there is an increase in production of the corticotropin-releasing hormone and of corticotropin, in addition to a reduction in the effect of the negative feedback mechanism caused by increased serum cortisol levels.[39-42]

Final Comments

The large number of different criteria adopted by the different authors demonstrates the non-existence of any consensus definition for the diagnosis of adrenal insufficiency in critically ill patients, particularly those in septic shock.

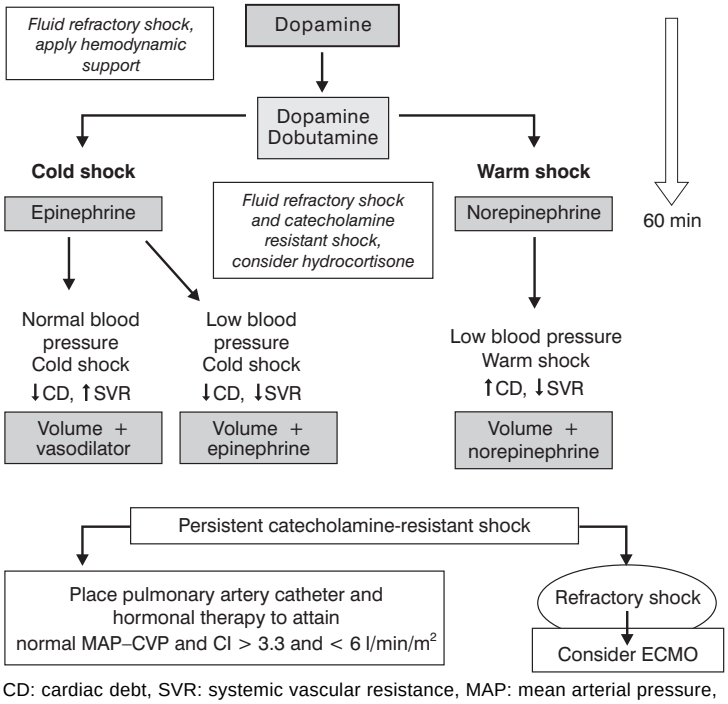
It appears, according to work by Annane et al.,[12] that a cortisol level above 34 µg/dl represents an intense response to sepsis, being related to severity and poor prognosis. The intensity of this response certainly has a relationship with the intensity of the stress, i.e. the severity of the sepsis in these patients. In contrast, the research papers cited in the subtitle of this review, the hypothalamus-pituitary-adrenal axis and cortisol secretion, demonstrate that among patients with critical diseases the average base cortisol level was found to be above 25 µg/dl and in work by Rivers et al.,[24] and also by Marik and Zaloga,[26] this point represented patients on vasopressors who responded or not to corticosteroid therapy, probably indicating that this group of patients had an adrenal response which was inadequate for the level of stress. We therefore believe that base cortisol levels above 25 µg/dl are the safest indication of patients in septic shock who have an adequate adrenal response.

We consider the ACTH test to be useful for identifying patients with relative adrenal insufficiency. We have opted for the low dose ACTH test, 0.5 µg/1,73 m², as we consider, based on the work presented above, that the high dose test, 250 µg/1,73 m², provokes a supraphysiological response, more than 100 times the normal response to stress, and can cause an adrenal response which is considered to be adequate but which does not in fact reflect reality. The criterion which appears most valid to us is the magnitude of the increase in cortisol levels post-test in comparison to the base value and we have opted for an increase of more than 9 µg/dl as the criterion for ruling out a diagnosis of relative adrenal insufficiency (occult). When performing this test we must take the pre-test cortisol level into account since with individuals who have very high cortisol levels, for example 45 µg/dl or more, it is possible that the adrenal gland is already working at its limit and is not capable of increasing production further; this increase may have an inverse relationship with base cortisol levels.[26,29] The synthetic ACTH adrenal stimulation test also provides a guide to which part of the axis is abnormal. Those patients whose base cortisol is below 25 µg/dl and who do not

respond to the synthetic ACTH adrenal stimulation test probably represent a group of patients with primary adrenal insufficiency. Within this group there will be individuals who would respond to the test with high dose ACTH, representing, who knows, the presence of resistance to the effects of ACTH. The group of patients with ACTH below 25 µg/dl, but with a normal response to ACTH stimulation at low doses, represents a group with a failure at the hypothalamus-pituitary portion of the axis, i.e. those with secondary adrenal insufficiency who present insufficient corticotropin or corticotropin-releasing hormone (CRH) production.[26]

In practice, supra-renal insufficiency should be suspected in all cases of septic shock that are refractory to adequate volume replacement and resistant to catecholamines. We should not forget that there are patients with an increased risk of supra-renal insufficiency including those with associated *purpura fulminans* and Waterhouse-Friedrichsen syndrome, those who have received previous long term treatment with steroids and those who have pituitary and adrenal abnormalities.

This review was not performed in order to evaluate the treatment of septic shock and, even less the benefits and risks of the use of glucocorticoids in the treatment of these patients. It is, nevertheless, worth pointing out that while studies published in the past[4,43] have not demonstrated beneficial effects from the use of corticosteroids in the treatment of septic shock, more recently published work has reported more rapid clinical recovery and reduced mortality rates among patients treated with steroids.[7-11] We have been using a pharmacological support system (Figure 1) very similar4 to that defined in the consensus document of the American College of Critical Care Medicine[20] and for suspected or confirmed adrenal insufficiency opt for the use a shock dose of hydrocortisone, i.e. 50 mg/kg of hydrocortisone as an attack dose followed by an infusion of 10-20 mg/kg over 24 hours.[44] Other authors prefer to use hydrocortisone in a stress dosage: 2 mg/kg on attack followed by a maintenance dose of 2 mg/kg/day. In pediatrics research is lacking which could define which of the dosages is the most appropriate. Base serum cortisol assay and the performance of the adrenal stimulation test with corticotropin with severe sepsis or septic shock patients can not only be of use when making the decision of whether or not to begin treatment with hydrocortisone but, and especially, in deciding whether or not to maintain the indication when its use has been based entirely on clinical parameters.



CD: cardiac debt, SVR: systemic vascular resistance, MAP: mean arterial pressure, CVP: central venous pressure, CI: cardiac index, ECMO: extracorporeal membrane oxygenation.

Figure 1 - Pharmacological support system for patient with septic shock. (modified from Carcillo et al., 2002)[20]

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