Nosography of systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome in internal medicine patients

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ABSTRACT

Sepsis is defined by the presence of at least two systemic inflammatory response syndrome criteria associated with an infection microbiologically or clinically evidenced. In Italy sepsis is responsible for 80,000 hospital admissions per year and, in the last decades, severe sepsis and septic shock cases are increasing, in correlation with the increased prevalence of multi-drug-resistant microbial strains. The predominant etiologic agents are Gram-positive and Gram-negative bacteria, but sepsis caused by fungi is increasing. The host response with both inflammatory and anti-inflammatory processes is responsible for organic failures, which complicate the syndrome, and for the susceptibility to secondary infections. The impairment of one or more organs or systems may be the onset clinical presentation. The organ dysfunctions complicating sepsis involve mainly cardiorespiratory system, kidneys, hemostatis and central nervous system. Fever or hypothermia, tachycardia, tachypnea, leukocytosis or leukopenia, elevated blood levels of lactate and procalcitonin, hypotension are diagnostically sensitive findings for sepsis. Definitive diagnosis requires isolation of the pathogen from blood sample or from the focus of infection. Therapeutic success against sepsis depends on the appropriate use of antibiotics, on the treatment of hemodynamic and respiratory disorder and on general supportive care. In some cases the use of activated protein C is to take in consideration.

Introduction

Sepsis is defined by an infection, proven (microbiologically evidenced) or clinically suspected, associated with systemic inflammatory response syndrome (SIRS) (Table 1).[1]

SIRS can have both infectious and non-infectious etiology (pancreatitis, burns, trauma, acute adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, occult hemorrhage, cardiac tamponade, anaphylaxis, drug-overdose).[1]

Severe sepsis is defined as sepsis complicated by hypotension and hypoperfusion and at least a sepsis-induced organ dysfunction, different from the one of primary infection (Table 1).[2]

Septic shock is defined as sepsis associated with arterial hypotension - systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) <65 mmHg or decrease in SBP of >40 mmHg - refractory to fluid bolus infusion and which requires vasopressors (Table 1) or hyperlactatemia.[3]

Epidemiology

In Italy sepsis is responsible for 70-80,000 hospital admissions per year. Severe sepsis occurs in 2.1% of all hospitalizations and septic shock in 3%.[4,5] This picture is essentially analogous to that of other Western countries: in the United States sepsis causes 2% of hospital admissions and more than 200,000 deaths per year.[6]

In the last decades, the incidence of severe sepsis and septic shock has increased and nowadays in the US, it is about 300 cases per 100,000 people.[7] The increased incidence can be related to the general population's

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older age, to immunosuppression, to the increased prevalence of multi-drug-resistant microbial strains.

Etiology

Sepsis may occur in response to each type of infection (Table 2).[8] However, the most frequent causes of sepsis is pneumonia.[9] Bacteremia is not essential for the development of the syndrome: blood cultures yield positive results only in one third of severe sepsis' cases and in around half of septic shock's cases.[10] Moreover, even if the etiologic agent can be identify by infected material cultures from a local site, one third of results from these cultures are negative.[11,12]

The predominant etiologic agents are Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common) and Gram-negative bacteria (*Escherichia coli, Klebsiella spp.,* and *Pseudomonas aeruginosa* prevail); together, they are responsible for about 70% of sepsis.[13,14] Nevertheless, sepsis caused by fungi is increasing (Table 2).[9]

Pathophysiology

The host responds to sepsis with inflammatory and anti-inflammatory processes in order to block the infection and to restore normal organic function. Both the inflammatory response and the anti-inflammatory one could result in being responsible for the contingent catastrophic consequences of sepsis.[15] One of the inflammatory response mechanisms, oriented to prevent infectious spread, is intravascular thrombosis, through the promotion of tissue factor expression and the inhibition of anticoagulant pathway protein C-protein S.[16] On the one hand, intravascular thrombosis associated with insufficient mitochondrial oxygen consumption and production of vasodilator molecules (nitric oxide, β-endorphin, bradykinin, platelet-activating factor, prostacyclin), can cause organ damage and multiple organ failure.[17] On the other hand, the anti-inflammatory response, aimed at tissue repair through neuroendocrine regulation (which induce inhibition of pro-inflammatory cytokines production),[18] reduced function of immune cells and inhibitions of pro-inflammatory transcription gene- induces susceptibility to secondary infections.[19,20]

Clinical manifestations

It is possible that during the initial phase of sepsis the patient does not immediately satisfy the diagnostic criteria, showing normal parameters in terms of core temperature, heart rate, respiratory rate, white blood cell (WBC) count. Nevertheless, generally the patient is feverish. The absence of fever or the presence of hypothermia is more common in the elderly, in alcoholics and in newborns.

Anyhow clinical manifestations of the syndrome overlap with signs and symptoms of underlying infectious disease. However, even in these cases, physical examination can highlight physical findings and allow the classification of the responsible infection.

Delirium can be a sign of sepsis in the elderly or

Table 1. Systemic inflammatory response syndrome, severe sepsis, septic shock.

SIRS*
Two or more of the following conditions:
Fever (oral temperature >38°C) or hypothermia (<36°C)
Tachypnea (>24 breaths/min)
Tachycardia (heart rate >90 beats/min)
Leukocytosis (>12,000/mL), leukopenia (<4000/mL), or >10% bands
Severe sepsis°
Sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection):
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation
PO_2/FiO_2<250 without pneumonia as infection source
PO_2/FiO_2<200 with pneumonia as infection source
Creatinine >2.0 mg/dL
Bilirubin >2 mg/dL
Platelet count <100,000/mL
International normalized ratio >1.5
Septic shock#
Sepsis with hypotension refractory to fluid resuscitation or hyperlactatemia:
Hypotension that persists despite resuscitation with 30 mL/kg of bolus intravenous fluid
Plasma lactate >1 mmol/L.

SIRS, systemic inflammatory response syndrome. *Definitions by the Consensus Conference ACCP/SCCM;[1] °*Adapted from Dellinger* et al., *2013;*[2] #*Adapted from Cawcutt and Peters, 2014.*[3]

in a patient with a preexisting neurologic impairment.[21] Acrocyanosis and ischemic necrosis of peripheral tissues are manifestations of a hemodynamic and procoagulative disorder. Other cutaneous lesions may reflect the action of bacterial toxins distributed hematogenously or the invasion of soft tissues by microorganisms themselves.[22,23] A generalized erythroderma suggests a toxic shock syndrome (*S. aureus, Streptococcus pyogenes*). Petechiae or purpura are typically associated with *Neisseria meningitidis* or *Haemophilus influenzae* infections. Generally ecthyma gangrenosum, with its typical bullous lesions, peripheral edema and necrotic center, indicates an infection caused by *P. aeruginosa*.

The impairment of one or more organs or systems may be the onset clinical presentation of sepsis syndrome. The organ dysfunctions complicating sepsis are especially against cardiorespiratory system, kidneys, hemostasis and central nervous system.[24]

In most cases, depression of myocardial function develops within 24 h, but in survivors returns to normal in a few days.[25]

The lung is one of the organs that are compromised earlier. Hyperventilation, respiratory alkalosis and hypoxemia are manifestations often present from the start. The abnormal capillary permeability and the absorption of liquid into lung tissue are responsible for two severe complications of sepsis: acute lung injury (ALI) and acute respiratory distress syndrome (ARDS),[26,27] both with acute onset, bilateral pulmonary infiltrates, no clinical evidence of increased left atrial pressure and with PO_2/FiO_2 ≤300 mmHg (ALI) and ≤200 mmHg (ARDS).[28]

Acute kidney injury (AKI) with oliguria and proteinuria has been observed in 50% of cases of severe sepsis and septic shock. The causes of AKI may be both pre-renal and intrinsic. Pre-renal AKI is caused by hypovolemia and hypotension;[29] intrinsic AKI may be secondary to kidney ischemia, a consequence of prerenal azotemia, but also to acute tubular necrosis and to interstitial nephritis due to inflammatory damage and all consequent to a generalized prothrombotic condition.

Nervous system involvement

During sepsis the level of consciousness is often altered. The central nervous system injury process is multifactorial and depends on cerebral vascular alterations, hypoxemia and alterations in acid-base equilibrium. In patients in whom sepsis lasts for weeks may be observed a polyneuropathy due to critical illness.[21]

Liver and gastrointestinal apparatus involvement

Frequently the hepatic function results slightly compromised because of microvascular alterations

Table 2. Common sites of infection in patients with severe sepsis by gender. Types of organism in culture-positive infected patients.

Common sites of infection in patients with severe sepsis by gender*		
Site of infection	**Frequency in male (%)**	**Frequency in female (%)**
Respiratory	41.8	35.8
Bacteriemia, site unspecified	21.0	20.0
Genitourinary	10.3	18.0
Abdominal	8.6	8.1
Device-related	1.2	1.0
Wound/soft tissue	9.0	7.5
Central nervous system	0.7	0.5
Endocarditis	0.9	0.5
Other/unspecified	6.7	8.6

Types of organism in culture-positive infected patients°					
Organism	**Frequency (%)**	**Organism**	**Frequency (%)**	**Organism**	**Frequency (%)**
Gram-positive		**Gram-negative**		Anaerobes	4.5
S. aureus	20.5	*Pseudomonas spp.*	19.9	Other bacteria	1.5
MRSA	10.2	*E. coli*	16.0	Fungi	
Enterococcus	10.9	*Klebsiella spp.*	12.7	*Candida*	17.0
S. epidermidis	10.8	*Acinetobacter spp.*	8.8	*Aspergillus*	1.4
S. pneumoniae	4.1	*Enterobacter*	7.0	Other	1.0
Other	6.4	Other	17.0	Parasites	0.7
				Other organism	3.9

**Adapted from van Gestel* et al., *2004*;[8] °*Adapted from Vincent* et al., *2009*.[9]

and liver inflammation. Cholestatic jaundice due to hepatocellular and canalicular dysfunction may precede other signs of sepsis. Acute liver failure is rare and generally it is a consequence of the hemodynamic disorder secondary to prolonged shock, hypovolemia and decreased hepatic blood flow. Liver function tests return to normal with resolution of the infection.[30] Gastrointestinal complications are to be related to motility disorder from hypoxic damage and inflammation and may occur with nausea, vomiting, diarrhea, and, alternatively, ileus generally reversible.[31] Ischemic bowel necrosis may complicate prolonged shock. Upper gastrointestinal bleeding may be the manifestation of stress ulcer.[32]

Adrenal cortex involvement

In severe infection cortisol secretion is increased with loss of normal circadian rhythm.[33,34] Stimulation of the hypothalamic-pituitary-adrenal axis is due to the action of high circulating levels of cytokines, which also determine tissue sensitization to cortisol.[35] However, during the course of severe infection many factors tend to inhibit steroid response until steroid adrenal insufficiency. In septic patients is possible to observe adrenal hemorrhage and dysfunctions. Moreover elevated levels of inflammatory cytokines can directly inhibit cortisol synthesis and induce a systemic and tissue resistance to it.[36] From a clinical point of view, adrenal insufficiency can be suggested in a septic patient who presents asthenia, anorexia, nausea, vomiting, diarrhea, confusion and a coexistent hemodynamic instability,[37] hyponatremia, hyperkalemia and hypereosinophilia.

Laboratory parameters

Characteristically, a complete blood count may show normocytic anemia and leukocytosis (WBC >12,000/μL) associated with a left shift and evidence of bands; eventual leukopenia (WBC <4000/μL) expresses a worse prognosis. Trombocytopenia (platelet <50,000/μL) has been observed in 10-30% of cases and reflects intravascular coagulation secondary to endothelial dysfunction. Thrombocytopenia, in association with other laboratory values as prolongation of the prothrombin time and the activated partial thromboplastin time, hypofibrinogenemia and antithrombin III deficiency, indicates ongoing disseminated intravascular coagulation. Blood smear may show the presence of schistocytes.[38] Furthermore it might be detected hyperglycemia, more frequent in diabetic patients, which can evolve in ketoacidosis favored by hypotension; occasionally, hyperglycemia may be preceded by hypoglycemia, caused by an insufficient glycogenesis and an excessive insulin release.[39]

Serum albumin level declines for reduced hepatic synthesis and its dispersion in extravascular space.[40]

During early phase of sepsis, arterial blood gases show respiratory alkalosis, while in advanced sepsis it might be observed anion gap metabolic acidosis because of lactic acid accumulation.[41]

The electrocardiogram is not specific. Generally it shows sinus tachycardia and nonspecific ST-T wave abnormalities.

The chest radiography may show bilateral infiltrates caused by ALI or ARDS.[42]

Diagnosis

In patients with proven or suspected infections, diagnostically sensitive findings for sepsis are fever or hypothermia, tachycardia, tachypnea, leukocytosis or leukopenia; diagnosis is further suggested by an acutely altered mental status, thrombocytopenia, elevated blood lactate level, hypotension (Table 3). Definitive diagnosis requires isolation of the pathogen from blood sample or from the focus of infection.[43] A proper blood culture requires a minimum of 10 mL of blood taken from different venipuncture sites.[44] Positive results are detected earlier in Gram-positive bacteria cultures (≥24 h) than in Gram-negative bacteria ones, which require longer incubation times (up to 7 days). Anyway, in many cases, blood cultures do not show any microbial growth. Culture of biological material from the primary site of infection or from infected cutaneous lesions, may be diagnostic.

Anyhow taking samples may not be simple, or the site of infection may be hidden. When indicated, it is necessary to send cerebrospinal fluid or samples taken from a central venous catheter or from other intravascular devices to the laboratory, in order to obtain a culture. Clinical detection of device-associated septicemia is difficult, at times. In patients with intravascular catheter, the rate of microbial growth in a culture of blood drawn through the catheter may be compared with that of blood drawn from a peripheral vein to assess the likelihood of catheter infection; a difference in the *time to positivity* of 2 or more hours suggests catheter infection.[45]

Therapy

Sepsis outcome depends on the time between clinical presentation and therapeutic intervention against infection and both hemodynamic and respiratory disorders, other than from the site of infection and comorbidities.

Antibiotic therapy has a better chance of success if started within an hour;[46] mortality increases progressively for each hour of delay in starting appropriate antibiotic treatment, empirical against both Gram-positive and Gram-negative bacteria (Table 4).[47,48]

Table 3. Diagnostic criteria for sepsis.

Documented or suspected infection plus ≥1 of the following	
General variables	**Hemodynamic variables**
Fever or hypothermia (body temperature >38.3°C or <36°C)	Arterial systolic pressure <90 mmHg or mean arterial pressure <70 mmHg or decrease in systolic pressure of >40 mmHg
Heart rate (>90 beats/min)	Mixed venous oxygen saturation >70%
Tachypnea (>24 breath/min)	Cardiac index >3.5 L/min/m^2 of body-surface area
Altered mental status	
Positive fluid balance (>20 mL/kg of body weight over 24 h)	**Organ-dysfunction variables**
Hyperglycemia (plasma glucose >120 mg/dL in patients without diabetes)	PaO_2/FiO_2 <300
	Urine output <0.5 mL/kg/h or 45 mL/h at least 2 h
Inflammatory variables	Increase in creatinine level of >0.5 mg/dL
Leukocytosis or leukopenia (white-cell count >12,000/mm^3 or <4000/mm^3) or >10% bands	INR >1.5 or aPTT >60 s
Plasma C-reactive protein >2 SD above the upper limit of the normal range	Paralytic ileus (absence of bowel sounds)
Plasma procalcitonin >2 SD above the upper limit of the normal range	Platelet count <100,000/mm^3
	Plasma total bilirubin >4 mg/dL
	Tissue-perfusion variables
	Plasma lactate >1 mmol/L
	Decrease capillary refill or mottling

INR, international normalized ratio; aPTT, activated partial thromboplastin time. *Adapted from Levy* et al., *2003*.[43]

Table 4. Empiric antimicrobial therapy for sepsis.

Clinical condition	Antimicrobial regimens		Bacterial pathogens
Immunocompeted adult	Piperacillin/tazobactam, or*	4.5 g q6h	Community acquired Gram-negative bacteria
	Imipenem-cilastatin, or	0.5 g q6h	*Staphylococcus aureus*
	Meropenem, or	1 g q8h	Gram-positive cocci (*Group A-β hemolitic Streptococcus* that produces pyrogenic exotoxin)
	Cefepime, or	2 g q12h	
	Ceftazidime plus	1 g q8h	
	Vancomycin, or	15 mg/kg q12h	
	Teicoplanin	6 mg/kg q8h, then q12h	
Inpatient	Piperacillin/tazobactam, or*	4.5 g q6h	Gram-negative bacilli (*Enterobacteriaceae, Pseudomonas aeruginosa*)
	Imipenem-cilastatin, or	0.5 g q6h	*Staphylococcus aureus* (MRSA)
	Meropenem, or	1 g q8h	*Coagulase-negative Staphylococci*
	Cefepime, or	2 g q12h	
	Ceftazidime plus	1 g q8h	
	Amikacin, or	15 mg/kg qd	
	Ciprofloxacin, or	400 mg q12h	
	Levofloxacin plus	500-750 mg q12h	
	Vancomycin, or	15 mg/kg q12h	
	Teicoplanin	6 mg/kg q8h, then q12h	
Neutropenic patient (absolute neutrophil count <500/μL)	Piperacillin/tazobactam, or*	4.5 g q6h	Gram-negative bacilli (*E. coli, Klebsiella spp., Pseudomonas spp.*)
	Imipenem-cilastatin, or	0.5 g q6h	Enterococcus (*E. faecium, E. faecalis)*
	Meropenem, or	1 g q8h	Gram-positive cocci (MRSA, *MR-Coagulase-negative Staphylococci)*
	Cefepime, or	2 g q12h	
	Ceftazidime plus	1 g q8h	
	Tobramycin° plus	5-7 mg/kg qd	
	Caspofungin#	70 mg loading dose then 50 mg qd	
Splenectomized patient	Cefotaxime, or	2 g q6-8h	*Streptococcus pneumoiae*
	Ceftriaxone, or	2 g q12h	*Klabsiella pneumoniae*
	Cefepime	2 g q12h	*Haemophilus influenzae*
			Neisseria meningitidis
Addicted patient	Vancomycin, or	15 mg/kg q12h	*Staphylococcus aureus* (MRSA)
	Teicoplanin, or	6 mg/kg q8h, then q12h	Gram-negative bacilli§
	Oxacillin plus	2 g q6h	
	Gentamicin	3-5 mg/kg qd	

*If the patient is allergic to β-lactam drugs, use ciprofloxacin or levofloxacin plus clindamycin; °add vancomycin or teicoplanin if the patient: i) has an indwelling vascular catheter, ii) has received quinolone prophylaxis, iii) has received chemotherapy that produces mucosal damage; #add antifungal therapy if the patient is hypotensive or has been receiving broad-spectrum antibacterial drugs; §also consider *Candida* spp.

Antibiotic monotherapy is not inferior to antibiotic combination therapy, which is indicated only in sepsis associated with neutropenia or caused by *Pseudomonas spp*; in these latter cases aminoglycoside monotherapy is less effective than its association with an antipseudomonal β-lactam antibiotic (cefepime, ceftazidime, piperacillin-tazobactam, meropenem).[49,50] Antifungal therapy should be used only in patients at high risk for invasive candidiasis (septic patient who has received broad-spectrum antibiotics and parenteral nutrition, or who has been neutropenic for more than 5 days, or who has had long-term central venous catheter, or who has been hospitalized in an Intensive Care Unit for a prolonged period).[51]

After the first six hours, organic functions have to be revalued and de-escalation of the initial antibiotic therapy have to be considered, with the aim of preventing multi-drug-resistant organism emergency, reducing drug toxicity risk and costs.[52]

Most of the patients requires antibiotics for at least a week. Treatment's duration is usually influenced by the site of tissue infection, the adequacy of surgical drainage, the patient's underlying disease, the antimicrobial susceptibility of the bacterial agent.[53]

Table 5. Treatment of severe sepsis and septic shock - interventions to restore perfusion, respiratory support, general supportive care.

Interventions to restore perfusion
Begin goal-directed resuscitation during first 6 h after recognition
Begin initial fluid resuscitation with crystalloid and consider the addition of albumin
Consider the addition of albumin when substantial amounts of crystalloid are required to maintain appropriate arterial pressure
Avoid hetastarch formulations
Begin initial fluid challenge (≥30 mL of crystalloids per kilogram of body weight) in patients with tissue hypoperfusion and suspected hypovolemia
Continue fluid-challenge technique as long as there is hemodynamic improvement
Use norepinephrine as the first-choice vasopressor (MAP ≥65 mmHg)
If an additional agent is needed, use epinephrine
Add vasopressin (at a dose of 0.03 units/min) when weaning of norepinephrine, if tolerated
Avoid the use of dopamine except in carefully selected patients (*e.g.*, patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)
Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (*e.g.*, elevated cardiac filling pressure or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure
Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at dose of 200 mg/day
Target a hemoglobin level of 7 to 9 g/dL in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage
Respiratory support
Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS
Apply a minimal amount of positive end-expiratory pressure in ARDS
Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS
Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS
Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mmHG) to the fraction of inspired oxygen of <100, in facilities that have experience with such practices
Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated
Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion
Use weaning protocol
General supportive care
Use a protocol-specified approach of blood glucose management, with the initiation of insulin after two consecutive blood glucose level of >180 mg/dL, targeting a blood glucose level of <180 mg/dL
Use the equivalent of continuous veno-venous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload
Administer prophylaxis for deep vein thrombosis
Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding
Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 h after a diagnosis of severe sepsis or septic shock
Address goals of care (treatment plans and end-of-life planning)

MAP, mean arterial pressure; ARDS, acute respiratory distress syndrome. *Adapted from Dellinger* et al., *2013*.[2]

Treatment of hemodynamic disorder

Treatment of hemodynamic disorder is essential to re-establish tissue perfusion and recuperate organ damages. Cardiocirculatory resuscitation (Table 5) requests infusion of crystalloid (normal saline) with an initial bolus dose of 30 mL/kg, in 1-2 h. However, in order to avoid eventual hyperchloremic acidosis, it is possible to alternate normal saline with Ringer's lactate. To avoid pulmonary edema, the central venous pressure should be maintained between 12-18 cm H_2O, and diuresis should be kept at >0.5 mL/kg/h by continuing fluid administration and, if necessary, adding furosemide.

In about one-third of patients, hypotension and organ hypoperfusion respond to this treatment (SBP >90 mmHg, MAP >65 mmHg). If fluid resuscitation has not been sufficient, vasopressor therapy is recommended (Table 5).[54] Norepinephrine should be the first-choice. Dopamine is not recommended because it may promote the onset of cardiac arrhythmias.[55] If necessary, another vasopressor (epinephrine or vasopressin) may be added. Dobutamine is recommended if ongoing signs of hypoperfusion are present, despite adequate fluid therapy and initial vasopressors administration.[52,53]

In patients with refractory hypotension the administration of hydrocortisone (50 mg q6h) has to be considered; if clinical improvement occurs within 24-48 h, this treatment may be continued for 5-7 days before slowly tapering and discontinuing it.[2]

Red blood cells transfusion is recommended if hemoglobin concentration is ≤7 g/dL with a target level of 9 g/dL, unless ischemic coronary artery disease, acute hemorrhage or severe hypoxemia are present.[56] Erythropoietin is not recommended to treat sepsis-related anemia.

Respiratory support

Ventilator therapy is indicated for progressive hypoxemia, hypercapnia, neurologic deterioration or respiratory muscles failure (Table 5). Tachypnea is an indicator of forthcoming respiratory collapse (respiratory rate >30 breaths/min).

General supportive care

Septic patients may experience protein hypercatabolism and AKI, which may require intermittent hemodialysis and continuous veno-venous hemofiltration. However, nutritional supplement (enteral or parenteral) can reduce protein hypercatabolism (Table 5).

Prophylactic heparinization is indicated to prevent deep venous thrombosis in patients without active bleeding; if heparin is contraindicated, compression stockings or an intermittent compression device should be useful.

Insulin should be used to keep blood glucose levels <180 mg/dL (and at about 150 mg/dL), but it is necessary to monitor the patient in order to avoid the risk of hypoglycemia.

Other therapies

Even if using activated protein C increases bleeding risk, its use has shown an improved survival within 28 days in septic patients with an APACHE II (acute physiology and chronic health evaluation II) score ≥25.[57]

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