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Consensus Document

Consensus Document (SEMES-SEMICYUC) Recommendations on how to manage the initial and multidisciplinary diagnosis and treatment of severe sepsis in hospital emergency departments

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SEPSIS WORKING GROUP.

INTRODUCTION

The emergency and intensive care departments agreed to take on a project aimed at emergency staff and focussing on patient care in hospital observation areas. The common objective was to improve their understanding of severe sepsis diagnosis and treatment for adult patients in the aforementioned departments. This was essentially based on a Consensus Document (CD) that was drawn up about the process, which considers different aspects of sepsis and includes definitions, diagnostic tools, basic treatment methods for severe sepsis and septic shock and refers specifically to the use of early antibiotic treatment that is selected on the basis of the different variables studied. The aim is for this CD to reach as many emergency department employees as possible.

Despite the advances in antibiotic treatment and methods to modulate immune system response, sepsis continues to be linked to high mortality which can reach levels of 40% in cases of severe sepsis and septic shock. Furthermore, incidence rates are also on the increase. At present there is enough scientific evidence to prove that early and focussed application of a series of diagnostic and treatment measures, which include antibiotic treatment and haemodynamic support, significantly improve a patient's chances of survival. We also know that these measures are scarcely implemented in all hospital environments. Sepsis needs to be identified quickly and treated immediately as it forms part of a time-dependent group of diseases. Delays in diagnosing or treating these diseases has a negative impact on patient progress and therefore these conditions are of special interest to the emergency department, where the correct course of action may have a significant effect on the patient's prognosis. The epidemiological information that is available states that 30%-40% of sepsis cases that are dealt with by Intensive Care Units (ICU) come from the emergency department, although the exact incidence of sepsis in the emergency department is unknown because figures are clearly underestimated and patients are incorrectly classified. The Scientific Societies that are aware of this situation launched a campaign in 2002 called

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the "Surviving Sepsis Campaign". This was a campaign led by Intensive Care teams on both sides of the Atlantic with the participation of the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine who are focused on managing sepsis in medical centres, mainly in an Intensive Care environment. The Spanish Society of Emergency Medicine (SEMES) along with Spanish Society of Intensive Care Medicine and Coronary Care Units (SEMICYUC), became aware of the problem and developed guidelines that help make septic patients easier to identify and manage.

Among the requirements established for these guidelines was that they had to be geared towards to an emergency department environment with a time window that was restricted to the first "six" hours of managing the septic patient. It also had to take into account maximum levels of medical demand in its recommendations.

This CD specifically refers to the following concepts:

1. Sepsis is a disease linked to increased mortality.

2. Severe sepsis diagnosis is complicated and this delays starting treatment early on. Therefore it is necessary to increase the index of suspicion and use other tools in order to identify the disease.

3. Classifying the seriousness of the patient's condition.

4. Delays in administering antibiotics or in stabilising the patient, when this is indicated, are fundamental issues which should be emphasised.

5. Managing severe sepsis should be done on the basis of a consensus between a multidiscipnary group which is formed around an emergency physician and an intensive care physician.

6. Introducing sepsis as a medical condition.

The recommendations that come from a working group, which are structured as medical channels, will undoubtedly become a highly valuable tool for improving patient management within a time frame established by healthcare models that include professionals from different backgrounds. These models have proven to be effective when dealing with other conditions, although their implementation has been difficult. The current focus of septic patient management is on the emergency department which is the area with the most responsibility. The different areas represented in the consensus will provide us with a document which will have to be adjusted according to the local characteristics of each centre but that will undoubtedly make any plans for improvement easier to implement.

EPIDEMIOLOGY: SEVERE SEPSIS IN SPAIN

Severe sepsis is a difficult syndrome to classify, diagnose and treat. It is induced by an infectious process and involves changes in tissue perfusion and organ dysfunction. It is triggered by the entry of microorganisms or their toxins in the circulation system. Sepsis then causes inflammation and the body's defence mechanisms can no longer be self regulated. This causes a drop in the production of proinflammatory substances or inflammatory mediators that activate interrelated coagulation and fibrinolysis which either control the infection or allow it to progress into severe sepsis or septic shock.

Of patients that come to hospital emergency departments (HED) 10.4% are diagnosed with an infectious condition (most commonly respiratory in origin), of these 20.6% need to be admitted to hospital[1]. 5%-17% of those with an infectious condition are admitted to hospital, according to different sources of information[2,3]. The seriousness of the condition varies a great deal, from the majority which are non-serious cases to cases of severe sepsis and septic shock.

Although initially it was estimated that only 5.3% of infected patients could be classified as septic[1,4], in actual fact between 5% and 10% fulfil the "sepsis diagnostic criteria"[5], which means that there are around 50,000-100,000 cases/year in Spain, and of these it is estimated that around 30% develop into severe sepsis of septic shock. The incidence of these infectious conditions is increasing at a yearly rate of 7%-9%[6-8] because of different factors, like increased life expectancy which leads to a greater number of chronic conditions affecting the population, an increase in the use of invasive techniques, immunodepression caused by drugs, patients treated with chemotherapy, etc.

Sepsis is the most prevalent illness in the ICU and has a very high mortality rate estimated at around 97 cases/100,000 people/year for severe sepsis (although sepsis cases represent around 333/cases/100,000 people/year)[9]. Severe sepsis develops in 29% of sepsis cases and septic shock in 9%. More than half are dealt with outside the ICU[2,9]. Therefore, it is possible to estimate that there are around 45,000 cases of severe sepsis a year in Spain and 13,000 of these end in death[8]. There are 18,000,000 cases/year worldwide with 1,400 deaths/day. Mortality by severe sepsis stands at around 28% if we take into account patients that also come from other hospital departments including HED[9,10] and 35%-

54% if we focus on ICU studies[10,11]. According to data from the EDU-SEPSIS study, in Spain from October-December 2005, severe sepsis mortality was 47% and reached 84% in cases of septic shock. These mortality statistics are very high compared to other diseases such as acute myocardial infarction (AMI) or stroke. In fact, comparatively more people die from sepsis than from breast or colon cancer or as a result of a complication related to AMI. The economic cost per septic episode is estimated at around 10,000 euros which is much higher than the costs related to AMI[12].

From the time the microorganism enters the system, the tissue, blood or other bodily fluids it triggers a complex sequence of events in the host with the aim of combating the attack (which is not always successful), and, on occasions, this can lead to the deterioration of the patient's condition which consequently has a severe impact on their prognosis and increases morbidity and mortality. The development of these clinical events takes the patient from systemic inflammatory response syndrome (SIRS) to sepsis, "severe sepsis", "low blood pressure caused by sepsis", "septic shock"…and then finally to "multiple organ dysfunction syndrome" which is the last stage of the disease in terms of seriousness.

Therefore, the concept of sepsis and its after effects (organ failure and dysfunction) should be understood as a dynamic and continuous process of "sepsis stages" which increases patient morbid-mortality as it develops[13,14]. For that reason correct action should be taken early in order to reduce its impact and "prevent sepsis progression". This means that HED should make an effort to diagnose patients early, treat them immediately and obtain the appropriate bacteria samples during the first few hours in order to minimise mortality and prevent patients from reaching the stage of severe sepsis and septic shock. The "race to delay and revert the process" begins the moment the patient arrives at the HED and in some cases this is done successfully, if not the patient is transferred to the ICU. Therefore, the speed with which we confront the problem and make a suspected or confirmed diagnosis as early as possible, and implement the initial treatment methods for "resuscitation", will determine the patient's immediate and later prognosis[15,16]. The effect on mortality of delaying antibacterial treatment in severe sepsis/septic shock is well known; if the correct antibacterial treatment is administered within the first 30 minutes after diagnosis or between the first 9-12 hours, mortality can vary between 17% and 74%, respectively[16].

Although sepsis related deaths have decreased, the increase in sepsis incidence means that the absolute number of deaths caused by sepsis has gone up, which constitutes a significant medical problem on a worldwide scale.

The Surviving Sepsis Campaign (SSC) was created in 2002 to raise awareness about this problem, adopt specific measures and develop guidelines and facilitate their implementation. The European Society of Intensive Care Medicine, the International Sepsis Forum, the Society of Critical Care Medicine, and the American College of Emergency Physicians worked together to establish the main objective of reducing severe sepsis mortality by 25% in 5 years (2005-2009). In Spain this translates into saving the lives of over 3,000 people/year. In order to do this, clinical guidelines were established[17] in the form of "two basic action packages" that would be developed jointly. The "initial resuscitation" package should be completed in the HED within the first 6 hours that severe sepsis is suspected, which means that the relevant measures should be carried out as soon as possible in the HED in order to achieve the "resuscitation objectives"[15]. When the septic patient is identified the "severe sepsis code" (SSC) is implemented in the HED and fluid replacement therapy begins, a lactate analysis is carried out, a blood culture is taken, the first dose of antibiotics is administered and the ICU is notified.

The "second package" involves the measures that need to be taken within the first 24 hours. They can be grouped together in the following way[17-20]: 1. Initial resuscitation, 2. Treating the infection (includes diagnosing the location and isolating the microorganism, as well as administering antibacterial treatment and measures to eradicate the focus using surgery, if necessary); 3. Treating the sepsis (corticoids and activated protein C); 4. Support treatment.

Unfortunately, having evaluated all the data from the "EDU-SEPSIS-SURVIVING study" in Spain, we know that these methods are not being carried out correctly during the first 24 hours and that resuscitation techniques are performed in less than half of cases, which is quite alarming and means that we need to make an effort to raise awareness so that everyone takes the correct measures given that "a patient's life is at risk"[21]. A recent study[16] showed that only 50% of patients received the correct antibacterial treatment within the first 6 hours after the onset of low blood pressure. A clear relationship was established between the delay in initial antibiotic treatment and mortality.

DETECTING AND IDENTIFYING SEVERE SEPSIS PATIENTS. LOGISTIC ASPECTS

The basic elements in identifying sepsis: definitions

The development of the definition of sepsis

In 1991, the ACCP (American College of Chest Physicians) and the SCCM (Society of Critical Care Medicine)[4] organised a conference based on a general agreement to develop a wide range of definitions which would improve doctors ability to diagnose, monitor and treat sepsis and other aspects related to the disease. The general definitions established at that conference have been used extensively in practice and in clinical trials on treatment interventions.

Establishing definitions for a syndrome is essentially a flawed process which needs to be updated in accordance with new physiopathological ideas or new diagnostic tests. In 2001 a group of experts contemplated the need to re-evaluate sepsis definitions in the light of new advances. The SCCM, ACCP and various other American and European Intensive Care scientific societies sponsored the International Sepsis Definitions Conference in 2001[5]. The experts that attended formed subgroups in order to evaluate the usefulness of sepsis signs and symptoms, cell markers, cytokines, microbiology data and coagulation parameters for establishing a diagnosis.

The final conference report found no evidence to support a change in the definitions of sepsis but found that the signs and symptoms were more varied than the initial criteria had established in 1991, attributing greater importance to biomarkers for early sepsis diagnosis. A list of these signs and symptoms can be found in Table 1. Despite the definitions that have been outlined here, the terms do not include precise details about patients with sepsis. Our aim in the future is to develop a system which details sepsis progression (PIRO system) involving the stratification of patients depending on their septic predisposition (comorbidity, genetic factors, etc.), the infection (pathogens and focus, etc.), system response [SIRS, septic shock, C-reactive protein (CRP), interleukin (IL), tumour necrosis factor (TNF), procalcitonin (PCT), etc.] and the level of organ dysfunction (SOFA, apoptosis, etc.) that determine the stage of progression in septic patients.

Sepsis as a concept includes everything from SIRS to suspected or documented severe infection. Severe sepsis is characterised by either acute change in the functioning of one or more organs (haemodynamics, kidney, respiratory, liver, haematological or neurological function) or by poor tissue perfusion (hyperlactacidemia) or low blood pressure (transient or persistent).

Septic shock is defined as the presence of low blood pressure which does not respond to intravascular volume expansion and requires treatment with amine perfusion.

TABLE 1. Sepsis definitions[5]

Sepsis: Any documented or suspected infection with one or more of the following criteria:
- Fever (central temperature >38.3°C) or hypothermia (central temperature <36°C).
- Tachycardia >90 beats/minute.
- Tachypnoea >30 breaths/minute.
- Altered consciousness.
- Oedema or positive fluid balance >20 ml/kg in 24 h.
- Hyperglycaemia (plasma glucose >110 mg/dl) in the absence of diabetes.
- Leukocytosis (>12,000/mm^3) or leucopoenia (<4,000/mm^3) or normal count with >10% immature forms.
- High plasma levels of C-reactive protein or procalcitonin.
- $SvcO_2$ >70% or cardiac index >3.5 l/min/m^2.

Severe sepsis: septic episode associated with organ dysfunction, hypoperfusion or low blood pressure that can be attributed to sepsis.
- Hypoxemia with PaO_2/FIO_2 <300 mm Hg.
- Oliguria (diuresis <0.5 ml/kg/h during at least 2 hours).
- Creatinine increase >0.5 mg/dl or a value of >2 mg/dl.
- Coagulation disorder (INR >1.5 o aPTT >60 secs).
- Thrombocytopenia <100,000/mm^3.
- Hyperbilirubinemia (bilirubin >2 mg/dl).
- Hyperlactacidemia (>3 mmol/l or 24 mg/dl).
- Low blood pressure (SBP <90 mm Hg, ABP <70 or decrease in SBP >40 mm Hg).

***Septic shock*:** persistent low blood pressure which cannot be explained by any other cause other than sepsis and that does not return to normal despite resuscitation with the correct volume.

INR: International Normalized Radio; SvO_2: oxygen saturation of haemoglobin in central venous blood; SBP: systolic blood pressure; ABP: average blood pressure; aPTT: activated partial thromboplastin time.

Early detection algorithm and sepsis stratification

The following early detection protocol, that has been taken from the severe sepsis and septic shock management guidelines which forms part of the "Surviving Sepsis Campaign", is being put forward (Fig. 1).[17,19].

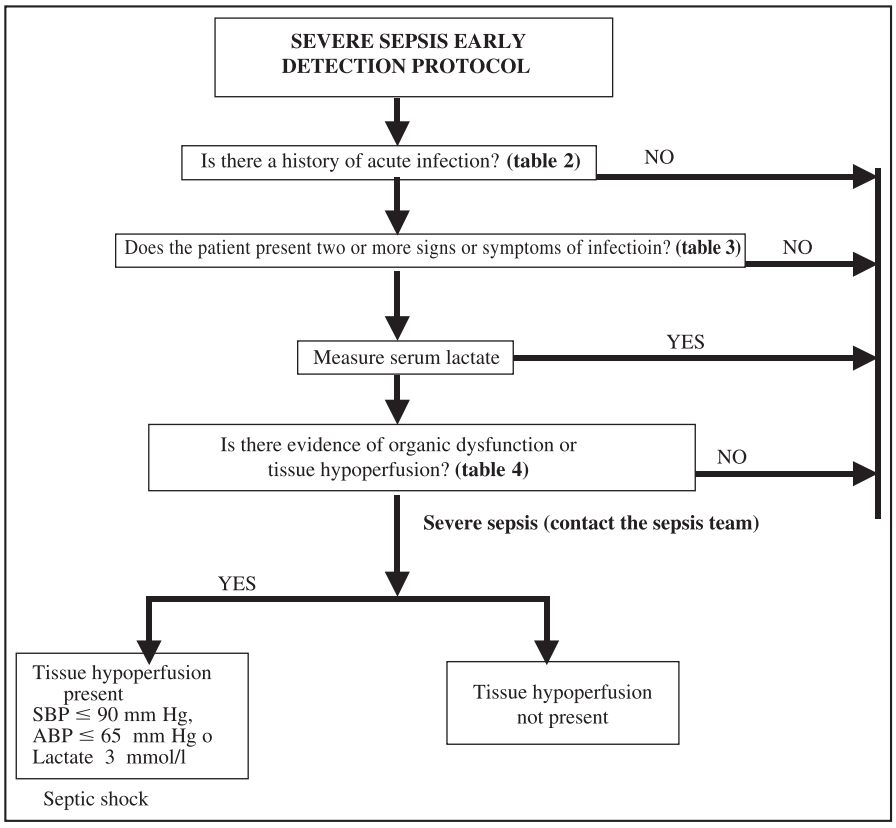


Figure 1. Early detection protocol and stratification of patients with sepsis. SBP: Systolic blood pressure; ABP: average blood pressure.

DIAGNOSING AND CONTROLLING THE FOCUS. BACTERIA TESTS. ANTIBACTERIAL TREATMENTS, WHICH ONE(S), WHEN...

Clinical and microbiological diagnosis

In the HED, initial awareness of the signs and symptoms in order to identify the focus of infection (Table 2) is crucial in patients with suspected sepsis, as well as collecting bacteria samples and choosing the empirical antibacterial treatment. Understanding the patient's medical profile and his/her history (immunosupression, recent surgery, dialysis, etc.) is useful in finding the focus and cause of the sepsis.

Among the additional tests that are carried out with the objective of establishing the extent of the infection and discovering the origin, a full blood count is recommended (blood count and white blood cell differential), and a coagulation test (platelets, D-dimer and fibrinogen), basic biochemistry [glucose, ions, calcium, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin and lactate], arterial or venous gasometry, urine sediment, a chest x-ray and an electrocardiogram (ECG). In some centres a routine CRP and PCT are carried out (Annex 1).

Microbiological diagnosis is based on evidence of the pathogen or its effects on the host's immune system within a specific medical context[22]. The cause of the infection must be established in the laboratory in order to administer the appropriate antibacterial treatment. In epidemiological terms it is important to establish the cause in order to understand its ecological niche.

The information that is provided by the laboratory will depend on the quality of the sample submitted. The sample should be obtained early (before antibiotic treatment), correctly (in sterile conditions, the sample should not be exposed to disinfectants, fresh samples are a priority, liquids and biopsies rather than cotton wool balls, and samples should preferably be from the edges of the wound) and adequate [the bacterial viability of some samples is limited because of physicochemical factors, at other times, for example in the case for cerebrospinal fluid (CSF), many tests are requested to obtain a small sample]. Serum samples need to be monitored afterwards in order to study seroconversion or the development of antibodies[22,23].

Bacterial samples are taken for the micibiological[24] diagnosis from all the areas that could be a focus for infection (sputum, CSF, bodily fluids, etc.). Blood cultures are exceptionally useful for diagnosing the cause and positive results are ob-

TABLE 2. Does the patient's history suggest a new infection?

Pneumonia/empyema
Meningitis
Infected wound
Urinary tract infection
Infection of the skin and/or soft tissues
Catheter infection
Acute abdominal infection
Bone/joint infection
Endocarditis
Infection of unknown origin

TABLE 3. Does the patient have two or more of the following signs and symptoms of systemic inflammatory response syndrome?

Fever ≥38.3°C
Hypothermia ≥36°C
Acute change in mental state
Tachycardia >90 bpm
Tachypnoea >30 bpm, or $PaCO_2$ <32 mm Hg
Leukocytosis (>12,000/mm^3)
Leucopoenia (<4,000/mm^3)
Hyperglycaemia (>120 mg/dl)

tained in 50% of sepsis cases. This should always be carried out irrespective of the focus of infection (recommendations on extraction techniques can be found in Annex 1). Other useful cultures which are easy to obtain are urine cultures, which are also the most common septic focus for patients over 65 (recommended samples and techniques for diagnosing the most common septic focus can be found in Annex 1).

ANNEX 1. Diagnosis of severe sepsis and septic shock

C-reactive protein (CRP) and procalcitonin (PCT). High levels suggest the existence of a systemic infection which is severe and/or bacterial rather than viral or inflammatory and therefore these indicators are useful because they help to manage and monitor the development of the condition. Levels of CRP ± 20 mg/l and PCT >2 ng/ml in patients with a clinical profile that indicates severe sepsis and leukocytosis and/or leucopoenia would suggest bacterial rather than viral origin. Levels of CRP <8 mg/l and PCT <0.5 ng/ml mean that the likelihood of bacteraemia or sepsis is below 1%-2% (except for patients with liver disease). Nowadays, PCT is considered the earliest and most reliable marker, although other very promising markers are under study such us IL-8 or the soluble factor TREM-1 (triggering receptor expressed on myeloid cells).

Blood cultures[23,34]. It is recommended that 2- 3 sets are extracted (1 set= aerobic bottle + 1 anaerobic bottle) per infectious episode before antibiotic treatment. It is recommended that this should be carried out at a temperature >38° or <36°C but can it can be done in any situation at the doctor's discretion. Samples should be extracted from different sites, under aseptic conditions (disinfecting the skin and the caps of the bottles using 70° alcohol, applying iodized alcohol to the skin for 1- 2 minutes and if possible, without touching the puncture site) and cultures from peripheral veins should be avoided. The recommended amount of blood is 10ml per bottle. The recommended time between extracting sets varies from 15 minutes to 2 hours, although in situations involving sepsis this can be reduced to 5- 10 minutes.

Microbiology samples depending on the focus of infection[22,23,34,35]

Respiratory focus. Blood (blood culture, serum for atypical bacteria and viruses) sputum (cultures, consider Gram staining), pleural liquid (Gram staining and cultures), urinary antigen analysis is recommended for detecting *Streptococcus pneumoniae and Legionella pneumophila.*

Abdominal focus. Blood (blood culture), consider imaging to rule out abdominal fluid collections and to evaluate the technical viability of percutaneous drainage. Purulent material obtained from the puncture or in surgery (Gram staining, cultures).

Urological focus. Blood (blood culture), spontaneous urine or urine obtained using a catheter or a suprapubic tube (urine culture), purulent material obtained via internal or external urological manipulation (Gram staining, cultures).

Skin and soft tissue focus. Blood (blood culture), tissue samples (Gram and cultures). It is preferable that the aspiration of fresh secretions from the ulcer, wound or biopsy be sent to the microbiology lab. Insufficient results are obtained from sterile cotton wool or a puncture/aspiration of 1cc of sterile saline solution.

Intravascular device focus. Blood (blood culture). It is recommended that blood cultures are extracted simultaneously from the tip of the catheter and from another site. Differences in blood cultures detected 2 or more hours after the growth in the catheter blood culture is obtained suggest that the infection is related to this device. The 5 cm tip of the extracted catheter (culture) should also be sent to the microbiology lab.

Central nervous system focus. Blood (blood culture), cerebrospinal fluid (CSF), (Gram staining, antigen analysis and cultures), material obtained via percutaneous puncture or stereotaxic surgery on a brain abscess if this is drained (Gram staining, Ziehl and cultures). Serum analysis may be useful for detecting human immunodeficiency virus (HIV) in patients with a brain abscess of unknown cause.

Empirical treatment

Antibiotic treatment should be given to the patient early (within the first hour of establishing the condition if possible[16,25]) and should be administered effectively (incorrect or delayed treatment is directly linked to higher morbimortality). Establishing the focus of infection and the resistance profile of local bacterial flora will help us to select the best antibacterial treatment.

As a general rule, except in cases where the focus of the infection is clearly identified (treatment recommendations depending on the focus of septic infection are outlined in Annex 2), the recommendation is to use broad spectrum antibacterial drugs and downscale depending on the results of the cultures[17,24-26]. Third generation (ceftriaxone, cefotaxime, ceftazidime) and fourth generation cephalosporins (cefepime), carbepenems (imipeneme, meropeneme) and penicillin with penicillinases (piperacillin-tazobactam) are the most commonly used antibiotics. Sometimes combinations of different antibacterial treatments can be used with the aim of broadening the spectrum (in polymicrobial infections), achieving synergism (in immunodepressed patients with infections) or reducing the number of resistant strains (in infections caused by multiresistant pathogens). Therefore, antibacterial treatment should include drugs that cover a broad spectrum and can be given to patients with the following risk factors: patients that have received 4 or more cycles of antibacterial drugs in the last year, previous colonisation by multiresistant bacteria (sputum, ulcers, etc.), maximum expiratory volume per second (MEVS) <30% in chronic pulmonary obstructive disease (CPOD), recent hospitalisation for a period of ≥5 days, high local prevalence of resistant bacteria, immunosuppressive treatment or illness, patients from care homes, IV antibiotic treatment, urological manipulations and/or treatment of ulcers at home and dialysis within the last 30 days[27,28], which would justify the empirical use of glycopeptides (vancomycin, teicoplanin), streptogramine (quinupristine, dalfoprsitine) or oxazolidinone (linezolid)[17,24-26].

Controlling the focus

The focus of infection, which we are trying to eradicate using infection control techniques, should be analysed in all patients with severe sepsis. Once the focus has been found we can begin to use control techniques in order to eradicate the bacteria and consequently control the condition[29]. These techniques include draining abscesses and fluid collections (thoracocentesis for empyemas, decompression and drainage of urological obstructions, percutaneous abscess drainage and monitoring intraabdominal fluid collections using a CT scan, etc.), surgical removal of dead tissue (fasciotomy for necrotising fasciitis, surgery for tubo-ovarian abscesses, nephrectomy for emphysematous pyelophritis, surgical cleaning for pressure ulcers, etc.) and the extraction of infected devices (catheters, prosthesis, etc.). Recommendations for controlling the focus of infections can be found in Annex 3.

ANNEX 2. Empirical treatment of the focus of infection in severe sepsis and septic shock

Respiratory focus. 3rd or 4th generation cephalosporins + respiratory quinolones[36,37].
Abdominal focus. Carbapenem (imipenem, meropenem) or piperacillin-tazobactam, or 3rd-4th generation cephalosporins + metronizadol, or aztreonam + metronidazol, or quinolone + metronidazol[38].
Urological focus. 3rd-4th generation cephalosporins, or quinolone, or antipseudomonal penicillin, or carbapenam ± aminoglycoside[39].
Skin and soft tissue focus[40]. Impetigo and cellulitis: 1st generation cephalosporin (cefazoline) or amoxicillin/clavulanic acid or clindamycin. Infection of a surgical wound: abdominal or genitourinary (carbapenem, piperacillin-tazobactam or quinolone + clindamycin). Not abdominal [1st generation cephalosporin (cefazoline), cloxaciline]. MRSA infection: Glycopeptide, oxazolidinone (linezolid), cotrimoxazol. Necrotising fasciitis: not isolated, no mixed flora (piperacillin-tazobactam or carbapenem + clindamycin ± ciprofloxacine), *Staphylococcus pyogenes* (penicillin +clindamycin, oxazolidinone or glycopeptide as an alternative.)
Unknown focus. Carbapenem (imipenem or meropenem) taken with vancomycin or linezolid. If the patient has previously received antibiotic treatment we should consider adding amikacin. Patients with an anaphylactic type allergy to penicillin can be administered amikacin and/or a fluorquinolone treatment.

MRSA: Methicillin resistant *Staphylococcus aureus.*

ANNEX 3. Strategies for controlling the focus of infection in severe sepsis and septic shock[29]

General measures. The aim is to eradicate the focus of infection in all patients with severe sepsis using control techniques: draining the abscess, removing infected necrotic tissues and extracting infected devices. Any control method that allows complete extraction and causes minimum trauma to the patient should be considered ultrsound/CT-guided percutaneous drainage may be effective in surgical drainage if feasible).
Once the focus of infection is identified, the control measures should begin immediately after the initial resuscitation. Intravascular devices that may be the cause of severe sepsis should be removed, before inserting another vascular access device in order to prevent this being colonised as well.

Chest infections. *Complicated pleural effusion:* insert a chest tube when thoracocentesis shows any of the following characteristics: pus, positive Gram staining or positive cultures, pH <7.20 or pH 0.15 U below arterial or glucose <40 mg/dl.
Pulmonary abscess: analysis of the abscess should be evaluated by inserting the ultrasound/CT-guided percutaneous drain in unstable patients. If this fails, surgical lobectomy of the affected area should be carried out.
Mediastinitis: once the diagnosis is confirmed thoracotomy should be carried out in order to remove tissues and drain the area.

Abdominal infections: peritonitis caused by perforation of the hollow viscus require definitive surgical control in order to eliminate leakage of contents from the intestine into the abdominal cavity. The surgical technique used depends on where the perforation is located and its size.
Intestinal ischemia: an intestinal stroke is a surgical emergency requiring intestinal resection, given that intestinal gangrene invariably causes death. Mesenteric blood flow should be re-established in patients with intestinal ischemia unaccompanied by stroke by embolectomy or mesenteric bypass.
Infected pancreatic necrosis: surgical removal is required.
Biliary sepsis: cholecystectomy or percutaneous cholecystectomy should be carried out patients with acute gangrenous cholecystitis. Cholangitis requires decompression of the biliary tree using endoscopic retrograde cholangiopancreatography and papilotomy, transparietohepatic biliary drainage or surgical drainage of the bile duct.

Urinary sepsis. In cases of obstructive pyelonephritis a percutaneous nephrostomy should be carried out or a urethral catheter should be inserted using cystoscopy. If urinary sepsis is complicated by a renal or perirenal abscess, percutaneous drainage should be carried out. Nephrectomy should be carried out in the case of gangrenous pyelonephritis.

Soft tissue infections. Removal of all necrotic tissues should be carried out as soon as possible in the case of necrotising soft tissue infection (necrotising fasciitis). Necrotising fasciitis should be suspected in all patients with general disproportionate deterioration in the appearance of cellulitis (RPC >15, >25,000 leukocytes/mm^3, Cr >2, Na <135) with crepitations or signs of cutaneous necrosis (blisters, ecchymosis). Ultrasound, CT scan and MRI are good at detecting involvement of the deeper tissues have been affected, although they are not very precise. All patients that undergo soft tissue removal because of necrotising infection should be surgically re-examined between 6 and 24 hours afterwards; which should take place sooner if the condition worsens[40,41].

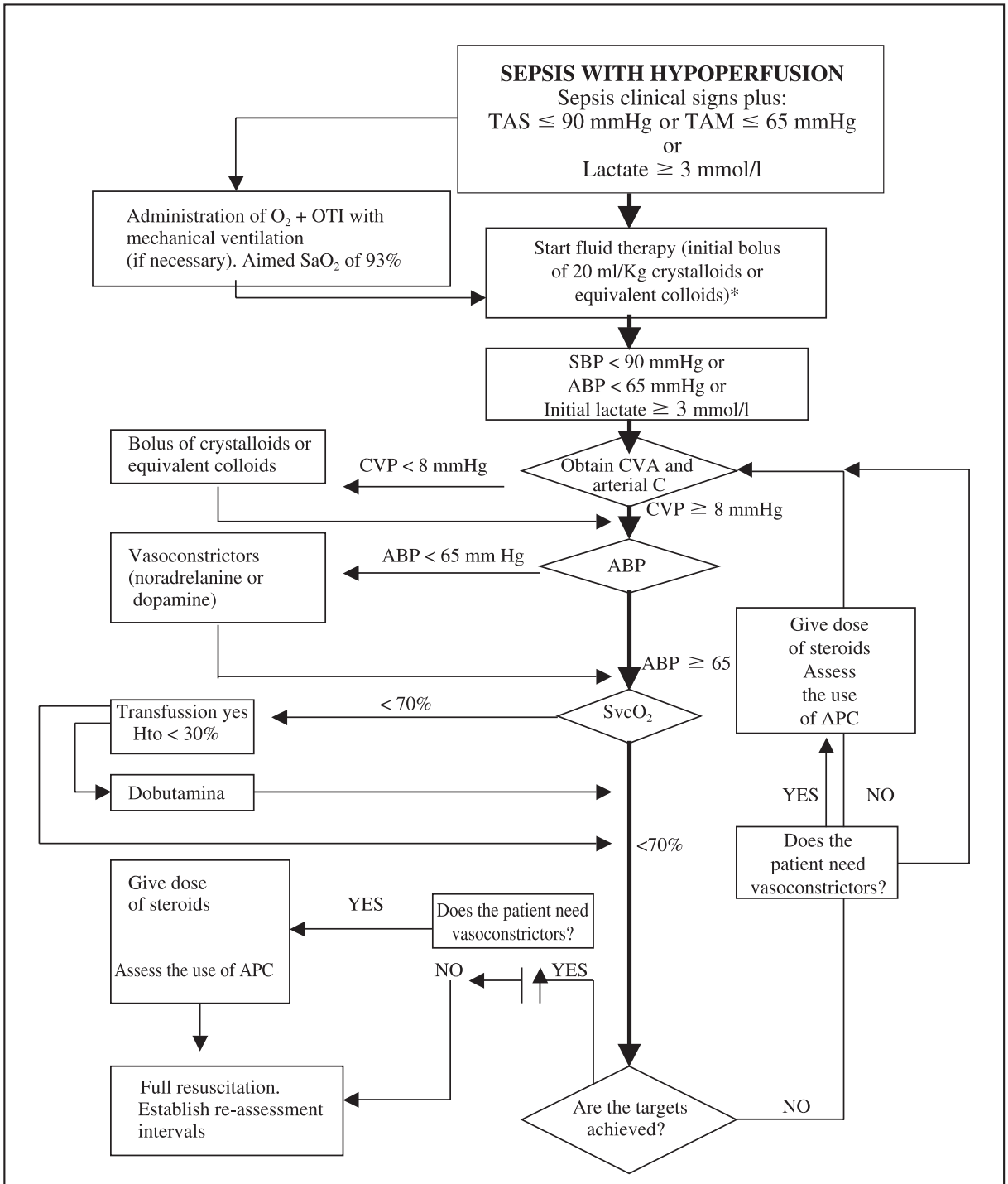
HAEMODYNAMIC SUPPORT AND OTHER MEASURES (FIG. 2)

Aim

The aim of haemodynamic support measures is to improve oxygen transportation in order to correct and prevent cell hypoxia. Cases of severe sepsis and septic shock should be considered emergencies and therefore, this needs to be done as quickly as possible[30]. The most important diagnostic variable is low blood pressure, although its absence does not rule out the presence of severe sepsis or the existence of hypoperfusion (Table 4). The clinical usefulness of central venous blood oxygen saturation has recently been demonstrated ($ScvO_2$) as a "variable guide" for correcting tissue hypoxia[30]. Therefore, the haemodynamic objectives for patients with severe sepsis and septic shock are to re-establish blood pressure and normalise SVO_2 by administrating volume, vasoactive amines and dobutamine.

Treating haemodynamic instability

First of all, situations involving a loss of fluids or haemorrhages which can cause low blood pressure for reasons that are not linked to severe infection should be rule out. When the patient has low blood pressure 500 ml-1000 ml (20 ml/kg) of crystalloids or 300-500 ml of colloids should be administer within 15 minutes. The volume load can be repeated depending on the response and the blood volume estimate, as well as the cardiac reserve and risk of



*In situations in which ABP is considered to be critically low, vasoconstrictors can be used at any stage of this algorithm.
OTI: orotracheal intubation, SaO_2: arterial oxygen saturation, SBP: systolic blood pressure, ABP: average blood pressure, CVC: central venous catheter, APC: activated protein, $ScvO_2$: central venous oxygen saturation. Hct: haematocrit.

Figure 2. Algorithm/series of actions for the haemodynamic management of severe sepsis and septic shock.

TABLE 4. Are any of the organ dysfunction criteria present which cannot be attributed to a chronic cause?

SBP <90 or ABP <65 mm Hg or a reduction of >40 mm Hg in basal blood pressure
Bilateral pulmonary infiltrates with increased inspired O_2 requirement in order to maintain O_2Sat >90%
Bilateral pulmonary infiltrates with PaO_2/FiO_2 <300
Creatinine >2 mg/dl (176.8 mmol/l) or diuresis <0.5 ml/kg/hour for >2 hours
Bilirubin >2 mg/dl (34.2 mmol/l)
Platelet count <100,000/mm^3
Coagulopathy INR >1.5 aPTT >60 secs.
Lactate > 3 mmol/l (27 mg/dl)

SBP: systolic blood pressure; ABP: average blood pressure; INR: International Normalized Radio; aPTT: activated partial thromboplastin time.

developing acute respiratory distress syndrome. There are no data that recommends the use of crystalloids over colloids or vice versa. The use of human albumin solution is not recommended.

Establishment of central venous access is recommended is when severe sepsis or septic shock is confirmed. Insertion of an arterial catheter to monitor pressure and arterial gasometry is very useful, however this technique depends on the availability of equipment and personnel.

Initial assessments

Assess ions, urea, creatinine, glucose, bilirubin, lactate, arterial gasometry and $SvcO_2$. Leukocyte, platelet, haemoglobin and haematocrit count. Samples for microbiological diagnosis: blood cultures and other relevant cultures (CSF, respiratory samples, exudates, etc.).

Haemodynamic stabilisation

The objective of initial haemodynamic stabilisation is systolic blood pressure (SPB) ≥ 90mm Hg or average blood pressure (ABP) of ≥ 65 mm Hg[17,30-32]. If central venous pressure is >8 mm Hg and ABP is <65 mm Hg then after 2-3 litres of crystalloids or 1 to 1.5 litres of colloids have been administered, vasopressors should be used. The use of noradrenalin is recommended and the initial dose should be around 0.04 µg/kg/min (8 mg of noradrenalin in 250 ml at 5 ml/hour) with 5 ml increments every 5 to 10 minutes depending on haemodynamic response. Continuous adrenalin infusion is not recommended. In cases of very low blood pressure (SPB <70 mm Hg or ABP <50 mm Hg) noradrenalin perfusion can be administered in the early stages of volume expansion, when CVP is still <8 mm Hg. Once SAB has been established at >90 mm Hg or ABP at >65 mm Hg, the noradrenalin infusion dose may be increased if high serum lactate levels persist or oliguria suggests poor tissue perfusion.

It has been suggested that "static" assessments of blood volume, such as CVP, pulmonary capillary pressure and other indicators of ventricular preload, are less reliable predictors of haemodynamic response to volume expansion compared to "dynamic" parameters[33].

Once we have established a CVP of >8 mm Hg and an ABP ≥ 65 mm Hg, $SvcO_2$ <70%, or serum lactate levels >3 mmol/l or other persistent signs of tissue hypoperfusion, may require dobutamine perfusion with vasopressor amines[17,32].

The transfusion of erythrocyte concentrates is only recommended with Hb <7 g/dl, except in cases of coronary disease, active haemorrhage or when serum lactate level are consistently >3 mmol/l (Tables 5 and 6) (Fig. 3).

Other measures

Oxygenation. Supplementary oxygen should be provided in order to maintain pulse oximeter saturation above 92%. The decision to proceed to intubate and connect patients with severe sepsis or septic shock to a mechanical ventilator should not be delayed in patients with tachypnoea >30/minute, the use of accessory muscles of respiration, desaturation levels <90% or in cases of injury or decreased level of consciousness.

Bicarbonate. Its use has been questioned but it may be considered for patients with an arterial blood pH reading of ≤ 7.15.

Glucocorticoids. It is necessary to administer intravenous hydrocortisone to patients undergoing chronic systemic steroid treatment. We may want to consider administering glucocorticoids to patients with refractory hypotension during volume expansion and high dose amine infusion. Hydrocortisone (50 mg intravenous bolus dose every 6 hours or 100 mg intravenously every 8 hours) modifies noradrenalin doses/response curves and increases BP, although it has not been proven that its use reduces mortality in cases of septic shock.

The first 24 hours. Other measures have been recommended during this period of time which include: low doses of corticoids, activated C protein if there are no contraindications and it is administered in accordance with standard protocols and to maintain glycaemia levels at <150 mg/dl. This should be considered depending on the patient's clinical status.

TABLE 5. Resuscitation measures in the first 6 hours of sepsis in the emergency department- Intensive Care Unit

1. Measure serum lactate* (in minutes)[30].
2. Obtain blood cultures before beginning antibiotic treatment[17] (within the first 2 hours)**.
3. Early antibiotic treatment***:
   3.1. Within 2 hours if the patient is seen in the emergency department.
   3.2. Within 1 hour if the patient is seen in the ICU and has not come from the emergency department.
4. If low blood pressure or >3 mmol/L (27 mg/dl) of lactate is present:
   4.1. Begin resuscitation with a minimum of 20-30 ml/kg of crystalloids (or equivalent dose of colloids)[32].
   4.2. Use vasopressors to treat low blood pressure during and after resuscitation with liquids (dopamine or noradrenalin).
5. If septic shock or lactate >3 mmol/l is present:
   5.1. Measure central venous pressure (CVP) and maintain CVP ≥ 8 mm Hg
   5.2. Measure central venous oxygen saturation ($SvcO_2$), and maintain $SvcO_2$ ≥ 70% using a transfusion if Hb <7 g/dl and/or dobutamine if hematocrit ≥ 30%. Alternatively, the mixed venous oxygen saturation can be measured by SvO_2 and maintained above 65%.

Evaluate CVP monitoring and $SVcO_2$ depending on the patient's clinical status, for example: in the absence of shock or lactate <3 mmol/l this is not necessary. *If there is no lactate, the base deficit can be used as an equivalent measure until this is resolved. **Obtain 2-3 blood cultures from separate sites without any delays between extractions in order to begin antibiotic treatment as soon as possible. ***Insert two peripheral IV lines and administer 500-1,000 ml of crystalloid in the first 30 minutes, 1,500-2,00 ml in the first hour and 500-1,000 ml/hour afterwards.

TABLE 6. The objectives of resuscitation measures in the first 6 hours

- ABP (average blood pressure) ≥ 65-70 mm Hg.
- CVP (central venous pressure) between 8-12 mm Hg (or 12-15 mm Hg if the patient is on a mechanical ventilator (MV) or has increased abdominal pressure).
- Diuresis ≥ 0.5 ml/kg/hour.
- SvO_2 (mixed venous saturation) or $SvcO_2$ (central saturation) ≥ 70%.

If septic shock or >3 mmol/l of lactate is present, maintain CVP at 8-12 mm Hg, maintain $SvcO_2$ ≥ 70% (or SvO_2 ≥65%) using a transfusion if Hb ≥ 7 g/dl and/or dobutamine if Hb >7 g/dl, up to a maximum of 20 µg/kg/min.

FINAL CONSIDERATIONS FOR MANAGING SEVERE SEPSIS IN HOSPITAL EMERGENCY DEPARTMENTS

Sepsis continues to be one of the main causes of death and the after effects linked to sepsis morbidity are also responsible for a significant health care burden. Neither has shown a decrease despite the advances in antibiotic treatment.

Sepsis mortality and morbidity can be reduced by using "action packages" that need to be introduced early. Sepsis has become a time-dependant condition (like AMI or acute stroke) and therefore its identification and management in the emergency department is of utmost importance.

Consequently, the following is recommended:

1. Identifying sepsis early is the first fundamental step in order to establish the initial treatment. Maintaining a high suspicion index when dealing with infected patients and using instruments to classify the seriousness of sepsis form the basis of early sepsis identification and structured patient management. The packages of the measures that need to be taken within the first 6 hours in hospital are centred on two basic objectives: controlling the infectious agent and maintaining tissue perfusion.

2. Antibiotic treatment for patients with sepsis within the first two hours should be the top priority in terms of treatment objectives.

3. Patients with low blood pressure or signs of tissue hypoperfusion (elevated lactate levels, $ScvO_2$ <70%, reduced diuresis) should receive volume overloads and the effectiveness of this should be checked by monitoring patient response. Unresponsive patients should be treated with vasoactive agents.

4. Patients with severe sepsis/septic shock should be treated in areas where they can be diagnosed correctly and monitored (ICU); however, their final destination, whether it be the emergency department or a conventional hospital ward, should not have any bearing on the package of measures that should be introduced. Coordinated management of these patients among the professionals from the aforementioned areas, with the collaboration of intensive care physicians, will improve the final outcome by using a multidisciplinary approach to deal with the complex condition of the septic patient.

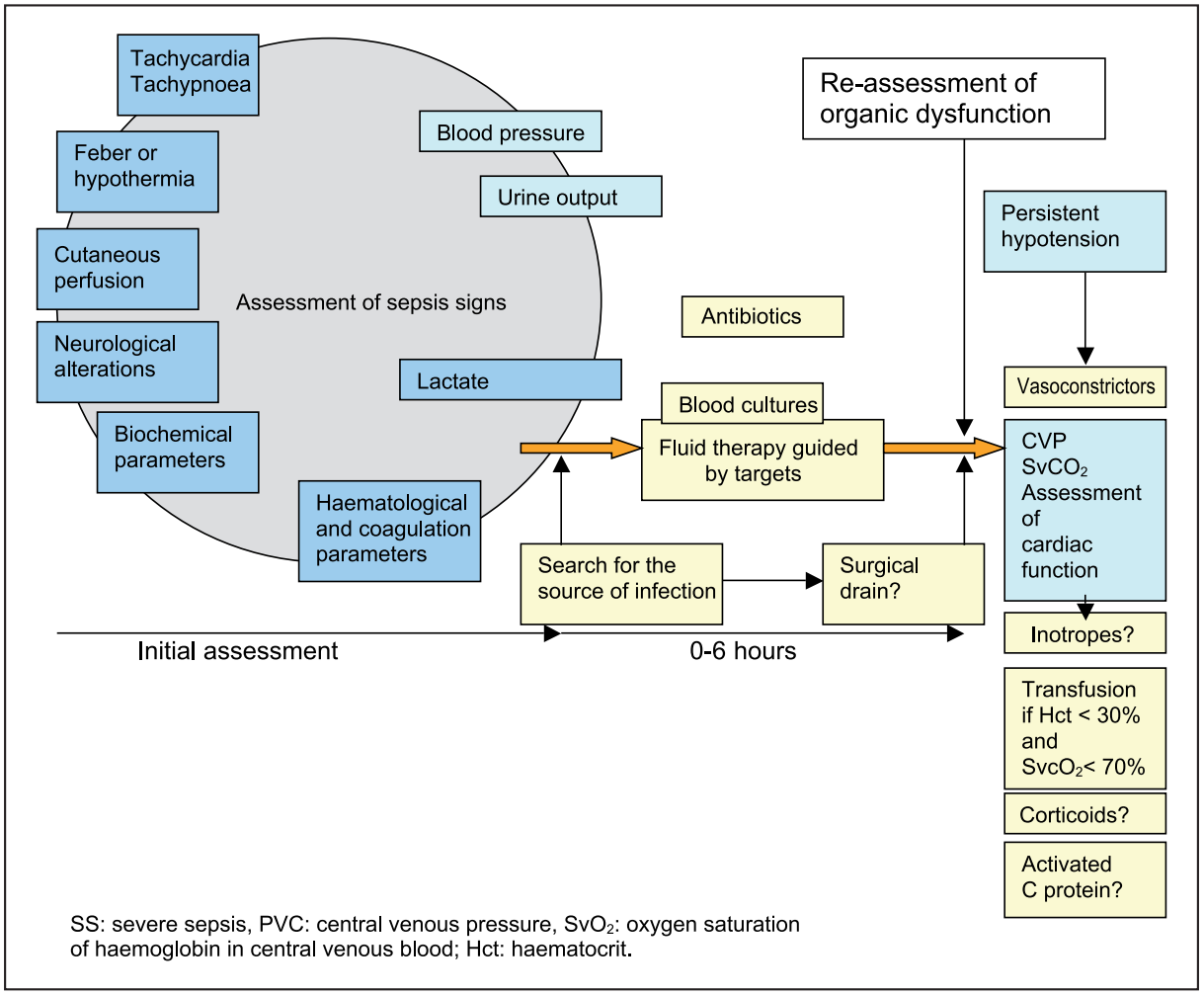


Figure 3. Diagnosis and initial treatment of severe sepsis[19].

5. It is essential therefore, that septic patients are attended as soon as they arrive in the HED. These patients are a top priority and should receive consensual and continuous care from both the emergency and intensive care departments, who will be working in accordance with established protocol in order to minimise the time spent working on the patient ("time is life") and make the correct decisions together, which will help to achieve the SSC objectives. The race against sepsis is a team effort and is won using the proposed measures quickly and early on involving multidisciplinary approach and the sepsis code, which is how other conditions have already been dealt with[42].

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