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A Noverview on Pathophysiology and Therapeutic Concept of Sepsis

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ABSTRACT

Infections represent a common health problem in people of all ages. Usually, the response given to them is appropriate and so little treatment is needed. Sometimes, however,the response to the infection is inadequate and may lead to organ dysfunction; this is the condition known as sepsis. Sepsis can be caused by bacteria, fungi or viruses and at present there is no specific treatment; its management basically focuses on containing the infection through source control and antibiotics plus organ function support. This article reviews key elements of sepsis management, focusing on diagnosis, biomarkers and therapy. The main recent advance in therapy is the strategy of personalized medicine, based on a precise approach using biomarkers to identify specific individuals who are likely to benefit from more personalized attention.

Keywords:

Bacteraemia;Criticallyillpatients;Pneumonia;Sepsis ;Septicshock.

I. INTRODUCTION

Sepsis is one of the most common causes of death among hospitalized patients in the intensive care unit (ICU). It is particularly difficult to diagnose in this setting because of the multiple comorbidities and underlying diseases that these patients present. **[1]**

The definitions of sepsis and septic shock focusing on the host's inflammatory response have remained unchanged since the first consensus conference held in 1991. Advances in the understanding of the pathophysiology of sepsis, which is characterized today as a host reaction to infection involving not only the activation of pro- and anti-inflammatory responses but also modifications in non-immunological pathways (cardiovascular, autonomic, neurological, hormonal, metabolic and clotting), have led experts to revise the definitions. In 2016, theSepsis-3 conference defined sepsis as a ''life-threatening organ dysfunction caused by a deregulated host response to infection'', and septic shock as a ''subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough tosubstantially increase mortality''. **[2]**

This is a narrativereviewwith the objective to update the advances in sepsis management.The first part focus on diagnosis, with a review of potential contribution of biomarkers, and the second part focus on advances in therapy.**[3]**

Definition

The word sepsis is derived from the Greek word for "decomposition" or "decay," and its first documented use was about 2700 years ago in Homer's poems. Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.**[23]**

II. ETIOLOGY

The etiology of sepsis is diverse, and clinical clues to various organ systems aid in appropriateworkupanddiagnosis.Itispertinent tobeableto distinguish betweentheinfectious and noninfectious causes of fever in a septic patient. The following are organ system–specific etiologies of possible sepsis:

Skin/soft tissue: Necrotizing fasciitis, cellulitis, myonecrosis, or gas gangrene, among others, with erythema, edema, lymphangitis and positive skin biopsy result.

Wound infection: Inflammation, edema, erythema, discharge of pus, with positive Gram stain and culture results from incision and drainage or deep cultures.

Upper respiratory tract: Pharyngitis, tonsillitis, or sinusitis, among others, with

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inflammation, exudate with or without swelling, and lymphadenopathy or positive throat swab culture or rapid test result.

Lower respiratory tract: Pneumonia, empyema, or lung abscess, among others, with productive cough, pleuritic chest pain, consolidation on auscultation, positive sputum culture result, positive blood culture result, rapid viral testing, urinary antigen testing (eg, Pneumococcus,Legionella),quantitativecultureofprotectedbrush,orbronchoalveolarlavage.

Central nervous system: Meningitis, brain abscess, or infected hematoma, among others, with signs of meningeal irritation, elevated CSF cell count and protein level, reduced CSF glucose level, positive Gram stain and culture results.

Cerebrovascular system: Myocardial infarction, acute valvular dysfunction, myocarditis, pericarditis, ruptured aortic aneurysm, aortitis, or septic emboli, among others, with elevated levels of cardiac enzymes, and imaging (ultrasonography, CT scanning, or MRI) of the chest, abdomen, and/or pelvis showing vascular involvement.

Vascularcatheters (arterial, venous): Redness or drainage at insertion site,positiveblood culture result (from the catheter and a peripheral site), and catheter tip culture after sterile removal.

Gastrointestinal: Colitis, infectious diarrhea, ischemic bowel, or appendicitis, among others, with abdominal pain, distension, diarrhea, andvomiting; positive stool culture resultand testing for toxigenic Escherichia coli, Salmonella, Shigella, Campylobacter, or Clostridium difficile.

Intra-abdominal: Renal abscess, pyelonephritis, pancreatitis, cholecystitis, liver abscess, intra-abdominal abscesses, or perforation, compromise, or rupture of an intra-abdominal or pelvic structure, among others, with specific symptoms and signs4; aerobic and anaerobic culture of drained abdominal fluid collections; peritoneal dialysis (PD) catheter infection with cloudy PD fluid, abdominal pain, deranged cell count, and positive PDfluidculture result.

Urinary tract: Cystitis, pyelonephritis, urethritis, or renal abscess, among others, with urgency, dysuria, pelvic, suprapubic, or back pain; urine microscopy showing pyuria or a positive urine culture result; urosepsis has been reported after prostatic biopsy. **[4]**

III. PATHOPHYSIOLOGY OF SEPSIS:

There has been a marked evolution in our understanding of the molecular pathobiologyand immunology of sepsis. Previously it was felt that hemodynamic manifestations of sepsis were primarily related to the hyperimmune host response to a particular pathogen. However, a large body of work on the molecular basis of sepsis has revealed a far more nuanced and complex interplay between the infectious agent and host that together produce the heterogeneous manifestations of sepsis. **[5]**

Innateimmunityandinflammatorymediators

The first step in the initiation of the host response to the pathogen is the activation of innate immune cells, constituted primarily by macrophages, monocytes, neutrophils, and natural killer cells. This occurs via the binding of pathogen-associated molecular patterns (PAMPs), such as bacterial endotoxins ins and fungal β-glucans to specific pattern recognition receptors, on these cells. Another source of such interaction are damage-associated molecular patterns (DAMPs) that may be intracellular material or molecules released from dead or damaged host cells, such as ATP and mitochondrial DNA. These bind to specific receptors on monocytes and macrophages such as toll-like receptors (TLRs), C-type leptin receptors, NOD-like receptors (nucleotide-binding oligomerization domain) and RIG-1 like receptors (retinoic acid inducible gene 1). **[6]**

This results in the activation of intracellular signal transduction pathways that cause the transcription and release of proinflammatory cytokines like TNFα, IL-1, and IL-6. In addition, some of the pattern recognition receptors, such as the NOD-like receptor group, can aggregate into larger protein complexes called inflammasomes that are involved in the production of crucial cytokines, such as IL-1β and IL-18 as well as caspases, which are involved in programmed cell death. Proinflammatory cytokines cause activation and proliferation of leukocytes, activation of the complement system, upregulation of endothelial adhesion molecules and chemokine expression, tissue factor production, and induction of hepatic acute phase reactants. In sepsis, there is an exaggeration of the above immune response resulting in collateral damage and death of host cells and tissues. **[7]**

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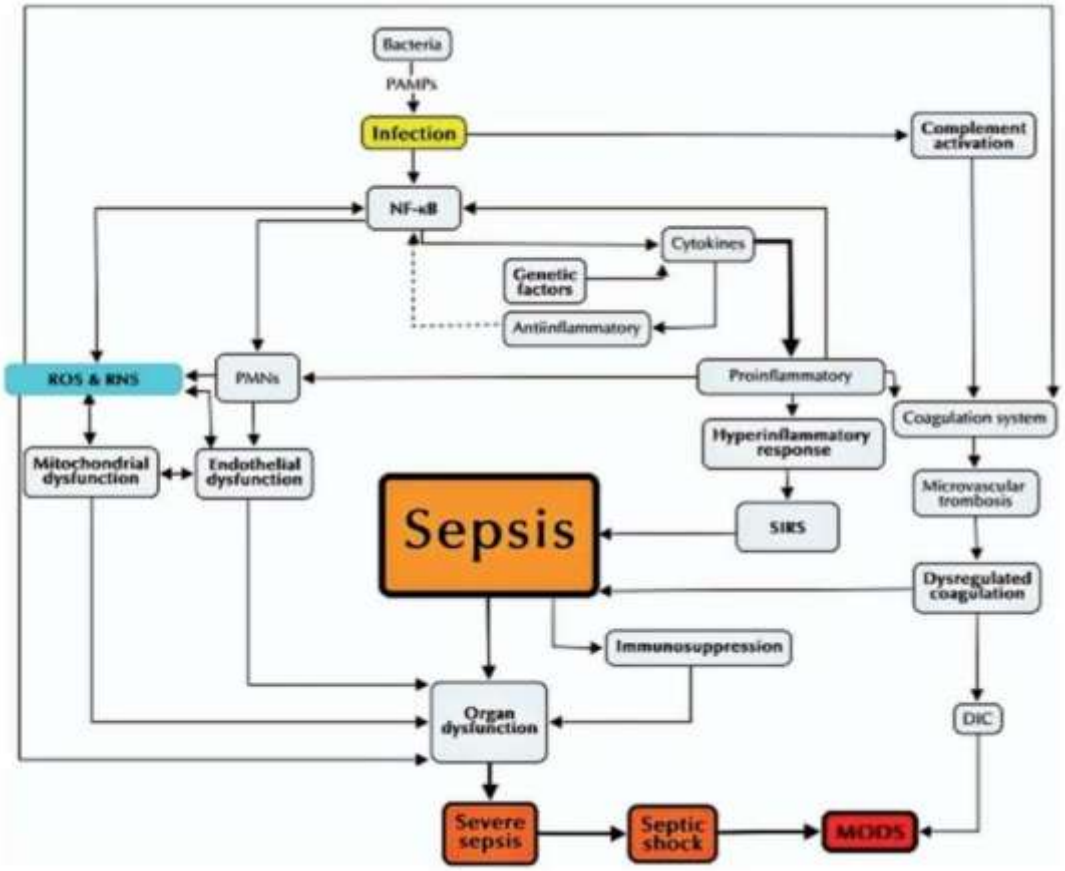
Figure1.Pathophysiologyofsepsis.



Dysregulationofhaemostasis

Insepsis,thereisanintersectionbetween theinflammatoryandhaemostatic pathways, with the simultaneous activation of both the inflammatory and the coagulation cascades. The spectrum of this interaction can vary from mild thrombocytopenia to fulminant disseminated intravascular coagulation (DIC). The etiology of the dysregulation of coagulation in sepsis is multifactorial.Thehypercoagulabilityofsepsisisthou ghttobedrivenbythereleaseoftissue factor from disrupted endothelial cells (other sources include monocytes andpolymorphonuclear cells). **[7]** In fact, in vitro experimental models of endotoxemia and bacteraemia have shown a complete inhibition of inflammation-induced thrombin production with the blockade of tissue factor.11 Tissue factor then causes the systemic activation of the coagulation cascade resulting in the production of thrombin, activation of platelets, and formation of platelet fibrin clots. These microthrombi can cause local perfusion defectsresulting in tissue hypoxia and organ dysfunction. **[8]**

In addition to the procoagulant effect described above, there is a depression of theanticoagulant effects ofprotein C and antithrombinthat wouldnormallytemper the coagulation cascade. Protein C is converted to its active form (activated protein C) by thrombomodulin whichitselfisactivatedbythrombin. ActivatedproteinCthenexertsananticoagulanteffect by degradation of factors Va and VIIIa acting in concert with activated protein S. It is also known to have potentanti-inflammatory effects via the inhibition of TNFα, IL-1β, and IL-6and limiting of neutrophil and monocyte adhesion to endothelium. In patients with severe systemic inflammation, such as in sepsis, there are decreased plasma levels of protein C, downregulation of thrombomodulin, and low levels of protein S thus allowing for the unregulated propagation of the coagulation cascade. **[9]**

In addition to the hypercoagulability

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described above, a reduction of fibrinolysis is also observed as a result of sepsis.13 As TNFα and IL-1β levels increase, tissue plasminogen activators are released from vascular endothelial cells. The resultant increase in activation of plasminisbluntedbythesustainedincreaseinplasminogenactivatorinhibitortype1(PAI-1). **[10]**

Table1.Definitionsofsepsis

SEPSIS – 1 (1991)	Sepsis – 2 (2001)	Sepsis – 3 (2016)	
Systemic Inflammatory response Syndrome (SIRS) • Temperature > 38 C or < 36 C • Heart Rate > 90 beats/min • Respiratory Rate > 20 breaths/min • WBC > 12,000/cu mm or < 4,000/cu mm OR > 10% immature forms (bands)	Suspected or documented infection and some of the following: • General Parameters: Temp > 38.3 C or < 36 C; heart rate > 90 beats/min or > 2 SD above normal for age; resp rate > 30 breaths/min; Altered mental status; significant edema or positive fluid balance (>20 ml/kg over 24 hr; Glucose > 110 mg/dL • Inflammatory parameters: WBC > 12,000 or < 4,000/cu mm; > 10% bands; plasma C-reactive protein > 2 SD above normal; Plasma procalcitonin > 2 SD above normal • Hemodynamic parameters: Systolic BP , 90 mm Hg; MAP <70 mm Hg; Systolic BP decrease > 40 mm Hg or < 2 SD below normal; Mixed venous oxygen saturation > 70%; Cardiac Index > 3.5 L/min/m2 • Organ Dysfunction Parameters: PaO2/FiO2 < 300; acute urine output < 0.5 ml/kg/hr or 45 ml/hr for at least 2 hrs; creatinine increase > 0.5 mg/dL; INR > 1.5; aPTT > 60 sec; Ileius; Platlets < 100,000 microL; Plasma total Bilirubin > 4 mg/dL • Tissue Perfusion Parameters: Lactate > 3 mmol/L; decreased capillary refill; mottling	Definition	Clinical Criteria
		Sepsis Screening: qSOFA of 2 or more	qSOFA: Altered mental status (GCS < 15); Systolic BP < 100 mm Hg; resp rate > 22 bpm
		Sepsis: life threatening organ dysfunction by dysregulated host response	Infection (suspected or documented) & SOFA increase of 2 or more
		Septic Shock: high mortality risk due to profound abnormalities in circulatory and cellular/metabolic function	Need of vasopressor for MAP ≥ 65 mm Hg and lactate > 2 mmol/L after fluid resuscitation

Immunosuppression

Interestingly, the initial proinflammatory state of sepsis is often superseded by a prolongedstate of immunosuppression.There is a decrease in the number of Tcells (helper and cytotoxic) as a result of apoptosis and a decreased response to inflammatory cytokines.14 Postmortem studies of ICU patients who died of sepsis demonstrated a global depletion of CD4+ and CD8+ T cells, most notably found in the lymphoid organs such as the spleen. Studies have also demonstrated decreased production of crucial cytokines such as IL-6 and TNF in response to endotoxin. In septic patients, neutrophils were found to have expressed fewer chemokine receptors, and there was diminished chemotaxis in response to IL-8. **[11-12]**

The above findings suggest that the immune system in a septic individual is unable to stage an effective immune response to secondary bacterial, viral, or fungal infections. Based on a study that showed that a low lymphocyte count early in sepsis is predictive of both 28-day and 1-year mortality, it has been postulated that early lymphopenia can serve as a bio marker for immunosuppression in sepsis.

Cellular,tissue,andorgandysfunction

The underlying mechanism behind tissue and organ dysfunction in sepsis is the decreased delivery to and utilization of oxygen by cells as a result of hypoperfusion. Hypoperfusionoccurs due to the cardiovascular dysfunction that is seen in sepsis. The incidence of septic cardiomyopathy varies from 18% to 60% in various studies. It is thought to be related to circulating cytokines, such as TNFα and IL-1β among others, which can cause depression of cardiac myocytes and an interference with their mitochondrial function. The most important feature of septic cardiomyopathy is that it is acute in onset and reversible. Second, the low left ventricular ejection fraction is accompanied by normal or low left ventricular filling pressures (unlike in cardiogenic shock) with increased left ventricular compliance. **[13]**

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Table2.Sequential(sepsis-related)organfailureassessment(SOFA)score.

Table 1. The Sequential Organ Failure Assessment (SOFA) score.

Respiratory system	Nervous system	Cardiovascular system	Liver	Coagulation	Kidneys	SOFA score
PaO2/FiO2 [mmHg]	Glasgow Coma Scale	Mean arterial pressure [MAP] OR administration of vasopressors required	Bilirubin [mg/dl] [µmol/L]	Platelets ×103/m	Creatinine [mg/dl] [µmol/L]; urine output	
>400	15	MAP > 70 mmHg	<1.2 [<20]	>150	<1.2 [<110]	0
<400	13–14	MAP < 70 mm/Hg	1.2–1.9 [20–32]	<150	1.2–1.9 [110–170]	1
<300	10–12	Dopamine ≤5 µg/kg/min or dobutamine [any dose]	2.0–5.9 [33–101]	<100	2.0–3.4 [171–299]	2
<200 with respiratory support	6–9	Dopamine >5 µg/kg/min OR epinephrine ≤0.1 µg/kg/min OR norepinephrine ≤0.1 µg/kg/min	6.0–11.9 [102–204]	<50	3.5–4.9 [300–440] [or urine output <500 mL/day]	3
<100 with respiratory support	<6	Dopamine >15 µh/kg/min OR epinephrine >0.1 µg/kg/min OR norepinephrine >0.1 µg/kg/min	>12.0 [>204]	<20	>5.0 [>440]; urine output <200 mL/day	4

MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment.

IV. EARLYSIGNS AND SYMPTOMS:

Earlieronthepresentationofsepsis,patientspresent withthefollowingvitalsignchanges:

- Fever,temperaturehigherthan38C,orhypothermi a,temperaturelowerthan36C.
- Tachycardia witha heart ratehigherthan 90beats per minutein adultpatientsor less than two standard deviations for age in pediatricpatients.
- Tachypnea with respiratory rate greater than 20 breaths per minute in adult patients or more than two standard deviations for age in pediatric patients.

SignsandSymptomsofSevereSepsis

Severe sepsis is defined as sepsis and end-organ dysfunction.At this stage, signsand symptoms may include:

- Alteredmentalstatus
- Oliguriaoranuria
- Hypoxia
- Cyanosis**[14]**

V. DIAGNOSIS OF SEPSIS

ClinicalDiagnosis

The Sepsis-3 definitions call for a new clinical tool to replace the criteria for systemic inflammatory response syndrome (SIRS) in identifying patients with sepsis. These criteria are non-specific, as they are not present in all patients with infection, and they do not necessarily reflect an abnormal host response. This is, for example, the case of fever: immunosuppressed patients do not always develop fever, so the infection is hard to detect. In contrast, critically ill patients have a certain degree of hyperthermia but may not present infection.**[15]**

The current recommendation for identifying both sepsis and septic shock is the use of the SOFAscore[Sequential(Sepsis-Related)OrganFailureAssessment].SOFAis a simple system, which uses accessible parameters in daily clinical practice to identify dysfunction or failure of the key organsas a resultof sepsis. It was developed at an expert meeting and theassessmentof physiological changes in response to septic attack was scored by consensus. Despite this initial subjectivity, the SOFA calibration is correct and properly adjusted to the subsequent evolution of the patient. Regardless of the initial SOFAscore, an increase during the first 48 hin the ICU predicts a mortality rate of at least 50%.

LaboratoryDiagnosis

Laboratory tests are required to help diagnose sepsis, distinguish it from other conditions, and evaluate and monitor organ function, blood oxygenation and the acid–base balance.

In the diagnosis of sepsis, the contribution of laboratory haematological, biochemical and microbiological test is essential. However, culture-based diagnosis is slow, and so, in recent years, major efforts have been made to find biomarkers

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that allow early diagnosis of this disease. In general, the markers that are studied are related to inflammatory mechanisms, in the hopethattheycouldcomplementorreplaceothersalrea dyinuse,suchasC-reactiveprotein (CRP) and procalcitonin (PCT). These tools cannot be used alone, and should complement careful clinical assessment and other laboratory data. Many studies looking for the ideal bio marker are underway, although progress is slow **[16-17].**

VI. MANAGEMENT:

Septic shock is a serious state of tissue hypoperfusion triggered by a systemic inflammatory response of infectious origin with impaired microcirculation and cytopathic hypoxia, which involves intense hypovolemia, vasodilation and cardiac dysfunction.

Given the high incidence, mortality rate and social impact of the condition, in 2002, the Surviving Sepsis Campaign (SSC) was set up to reduce sepsis-related mortality. The SSC pro posed a series of care bundles organized in a protocol of early and simple goals.**[18]**

The first, named ‘‘the 3-h severe sepsis resuscitation bundle’’, contains all the therapeutic steps to be performed within 3 h of the presentation of septic shock: measurement of lactate level, obtaining blood cultures before antibiotics, and administration of broad spectrum antibioticsand of crystalloid 30 ml/ kg for hypotension or lactate C 4mmol/L. The second part, ‘‘the 6-h septic shock bundle’’, contains all therapeutic steps to be performed within 6h of the presentation with septic shock: application of vasopressors (for hypotension not responding to initial fluid replacement) in order to maintain a mean arterial pressure (MAP) C 65 mmHg, measurement of central venous pressure (CVP) and venous oxyhemoglobin saturation (ScvO2) when hypotension persists despite volume replacement or initial lactate C 4mmol/L,and re-measurement of lactate if the initial level was high.

As for ‘‘the 24-h management bundle’’, some substantial changes have been introduced in responseto thepropoſalsputforwardinsubsequentstudies,suchas raisingthelevelofglucose to establish insulin infusion to 180 mg/ dl, and the withdrawal of the administration of recombinant-activated protein C (APCr). Only the controversy of adjuvant steroid therapy persists, remaining an indication for refractory shock in addition to adequate fluid resuscitation and vasopressor administration. **19**

Initial TreatmentofSepticPatient:‘‘TimeisLife’’

Early administration of broad-spectrum antibi otics and early, intense fluid intake are the basis for effective treatment of septic shock. Vaso pressors, although generally necessary, should initially be regarded as asecond-line treatment with clear criteria for their use, administrationof inotropic drugs and transfusion of packed red blood cells.

OxygenandMechanicalVentilation

The administration of oxygen via a mask or early endotracheal intubation is recommended in order to optimize and reduce oxygen consumption, by the increased work of breathing. It isalso recommended for the protection of the airway inthe case ofimpairedconsciousness.**[19]**

EarlyAntibioticTreatment

Distinguishing the infection origin is a priority, because it favours early antibiotic treatmentand/ or surgical control ofthe focus. Kumar et al. reported that every hour ofdelay in antibiotic administrationwasassociatedwithareducedsurvivalo f7.6%.Alargeretrospectivestudyof 17,990 patients with sepsis and septic shock found that delay in first antibiotic administration was associated with increase in the risk of mortality for each hour delay in antibiotic administration. One recent retrospective cohort study found that each hour until initial antimicrobial administration was associated with a 8.0% increase in progression to septicshock, and time to initial antimicrobial was also associated with in-hospital mortality.**[20]**

TransfusionofBloodProducts

Oxygen supply to the tissues depends on the level of haemoglobin. Transfusion isrecommendedinpatientswithsevere sepsiswhenhaemoglobinlevelsdescendbelow7 g/dL. **19**Critically ill patients generally have a better prognosis when blood transfusion is managed conservatively. It is recommended that levels be kept between 7 and 9g/dL, although this threshold rises in certain conditions such as myocardial ischemia, acute haemorrhage,refractory hypoxemia and lactic acidosis. **[21]**

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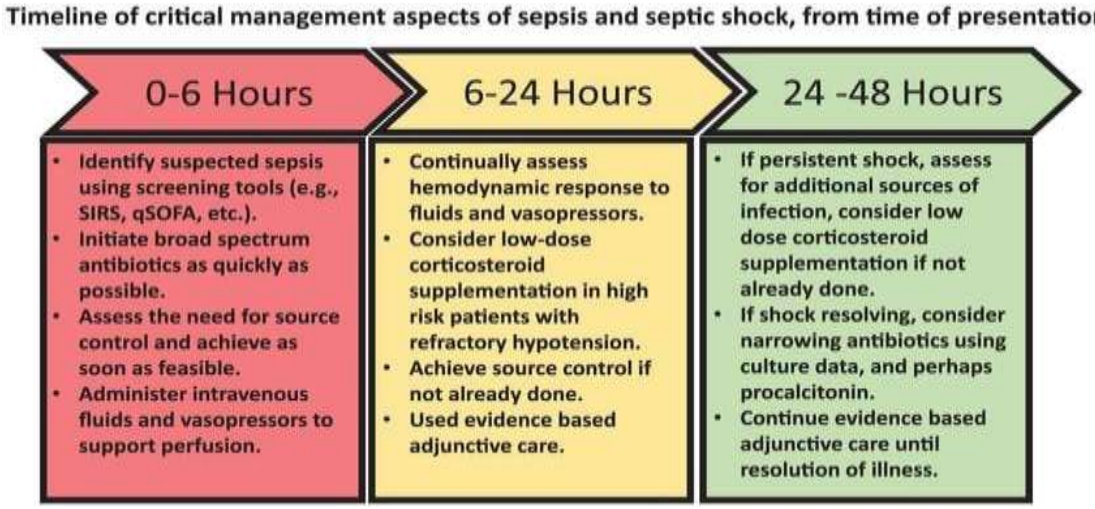
TreatmentofSepticPatientsintheLatePhase:OrgannDysfunctionSupport

After the first hours of septic shock, a late stage starts with a predominant presence of mul ti-organ dysfunction. AP is generally main tained with progressively higher doses of noradrenaline; less frequently, patients may present refractory hypotension, evolving to poor outcome .The addition of other vasoactive drugs to noradrenaline may be required (adrenaline, dobutamine or vaso pressin). Indeed, adrenaline could be adminis tered as rescue therapy in patients with refractory shockassociated with lowcardiac output asan alternative or in addition to nora drenaline.[22]



VII. CONCLUSION

In summary, sepsis remains a major health problem because of its high mortality andmorbidity. Identification and early treatment is crucial in order to deliver prompt, correct treatmentandincrease the chancesofsurvival.Currently, the diagnosisof sepsisfocuseson the use of biomarkers. Progress in this field has been slow; most efforts have been centered on single markers, but, given the complexity of the sepsis response, the main focus should be on combinationsofmarkers.Theuseofbiomarkersinthefuture,using‘‘omics’’toindividualize different subsets, will help improve the outcomes by improving diagnostic accuracy, reducing the time needed to identify the best treatment, and limiting unnecessary tests and treatments. Therapy remains based on source control, correct antibiotic prescription and supportive management.

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