ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY

Review Article

Five Key Points to Consider from a Practice Point of View when Sepsis is Suspected: A Pragmatic Approach for the First Six Hours

Fernando Martinez-Sagasti*

Department of Intensive Care, Hospital Clínico San Carlos, Madrid, Spain

***Corresponding Author**: Fernando Martinez-Sagasti, Department of Intensive Care, Hospital Clínico San Carlos, Madrid, Spain.

Received: February 04, 2020; **Published:** February 26, 2020

Abstract

Infection is a very common cause of attendance at the Emergency Departments. In some cases, a dysregulated host response to infection produces a life-threatening organ dysfunction syndrome known as sepsis according to the current definitions. This editorial will discuss the importance of being systematic and having a very high level of awareness to identify the septic patient as soon as possible. The new q-SOFA scale might be a useful and easy tool to perform at the bed side but neither substitute the SIRS criteria nor the SOFA score. A rapid blood gas test with lactate might stratify high risk patients while complete laboratory tests are available. Those patients with lactate > 2 mmol/L and mean blood pressure < 65 mmHg are in shock and must be promptly resuscitated with crystalloids. Looking for the site of infection as well as initiating antibiotics after taking blood cultures is of paramount importance

Keywords: *Sepsis; Septic Shock; SIRS; q-SOFA; SOFA; Lactate; Crystalloids; Source Control*

Introduction

The Third International Consensus Definitions Task Force (also known as "the new definitions of sepsis" or "Sepsis-3") [1] defined sepsis as a "life-threatening organ dysfunction due to a dysregulated host response to infection". Despite this simple definition, diagnosing sepsis is a challenging activity that all the attending physicians around the world have to face on a daily basis, particularly those who are working either at the Emergency Departments (ED) or at the Intensive Care Units (ICU).

Sepsis is one of the most common diagnoses at the ED which varies between 3% to 20% depending on the country and the definition used [2-5], but these figures might be underestimated because a considerable number of septic patients are not correctly identified from the beginning [6]. Failure to diagnose the septic patient has harmful consequences because it has been well established that the sooner the appropriate fluids and antibiotics are implemented, the better the result [7,8].

The "new definitions of sepsis" are about to turn four [1,9]. They intended to be more precise than the previous ones to facilitate the correct identification of the septic patient but some concerns have arisen, particularly in the validity of q-SOFA to predict in-hospital mortality in hospitalized patients with suspected infection [10].

Although there is an international consensus considering sepsis as an infection so severe that it produces organ dysfunction, the way in which organ dysfunction should be identified is more controversial [11].

After working for more than twenty five years in an ICU collaborating with the ED of my hospital and taking into account the latest guidelines [12] and definitions of sepsis and septic shock [13], I will discuss five essential points that every attending physician must address when facing a possible septic patient. It is very important to understand that, although I will split the work flow into five points for a better understanding, many of these points must be done simultaneously.

Suspecting infection: The importance of the SIRS criteria

Identifying signs and symptoms of infection is the first step in diagnosing sepsis and this seemingly simple thing is not always easy. The classical approach to this identification has been based on the Systemic Inflammatory Response Syndrome (SIRS) (Table 1). According to the previous definitions of sepsis [14], those patients having at least two of these four criteria should be screened for a potential infection.

Variable	Points
Fever ≥ 38°C or Hypothermia < 36°C	1
Heart rate > 90 beats/min	1
Tachypnea > 20 breaths/min or pCO_2 < 32 mmHg	1
Leukocytosis (WBC count > 12.000/mcL) Leukopenia (WBC count < 4.000 mcL) or Normal WBC count with greater than 10% immature forms	1

Table 1: *Systemic inflammatory response syndrome (SIRS).*
WBC: White Blood Cells.

Although it is true that presenting 2 of these 4 criteria is quite nonspecific for diagnosing an infection, this is its advantage when a patient is first evaluated. Given that sepsis is a very dynamic syndrome, it is better to identify a patient as potentially infected and later rule out sepsis because she/he does not develop organ dysfunction than the other way around.

The "Sepsis 3" definitions do not recommend SIRS as the standard approach, they encourage the evaluation of q-SOFA scale (Table 2) to those patients in the ED who are suspected of having an infection, so the question is: how can I suspect that the patient is suffering an infection but looking for the SIRS criteria and the source of infection?

Variable	Points
Respiratory rate, breaths per minute > 22	1
Systolic blood pressure < 100 mmHg	1
Altered mental status (Glasgow Coma Scale) ≤ 13	1

Table 2: *quick-SOFA (q-SOFA) score.*

This is why, in my opinion, every doctor has to check the four SIRS criteria as the first step in diagnosing an infection. Questioning the patient simultaneously about specific symptoms to identify the site of infection is mandatory.

You should keep in mind that misidentification of the infection site affects the result [15]. There are 6 main potential sites to check, so different complementary tests will be needed to clarify the anatomical site of infection depending on the signs and symptoms [16]:

a) The respiratory system will require a chest X-ray to rule out pneumonia.

b) The abdominal cavity is a difficult place to explore but an abdominal ultrasound may be very useful to rule out appendicitis, cholecystitis or cholangitis. Nevertheless, when diverticulitis or diffuse peritonitis are likely an abdominal computed tomography (CT) must be considered.

c) The genitourinary tract infection needs to perform a urinalysis and a renal ultrasound when obstructive uropathy is likely.

d) The skin and soft tissues infection is usually easy to identify when cellulitis or purulent abscess are present but fasciitis might be difficult to see. Those patients complaining of severe apparently disproportionate pain on the skin might suffer from necrotizing fasciitis. In these cases, a CT might be useful.

e) The bloodstream is other potential site, particularly when endocarditis is likely an echocardiogram must be performed. Some patients have central lines that may be the source of infection.

f) The central nervous system is the last main place to test. A lumbar puncture has to be done when there are signs of meningitis.

Identifying the site of infection might be especially difficult in elderly people who, very often, do not complaint of any particular focus related symptoms and they just seem to be less active and alert. Moreover, when you are in front of a patient who does not feel well, just complaining of very vague symptoms, think about an infection as the cause of that clinical situation.

Diagnosing sepsis: Stratifying severity to start fluid resuscitation

Once an infection has been diagnosed and while its site is being investigated, the severity of that infection must be rapidly evaluated. The presence of organ dysfunction defines sepsis, being its early recognition essential for a successful outcome. The "Sepsis-3" Task Force defines that those infected patients scoring 2 or more points on the q-SOFA scale have sepsis but those patients no scoring so high might have sepsis as well, so clinical examine and blood tests to quantify the SOFA scale (Table 3) must be determined before ruling out sepsis since having at least 2 points on the SOFA scale also defines sepsis.

	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory PaO_2/FiO_2 (mmHg)	> 400	≤ 400	≤ 300	≤ 200 (with RP)	≤ 100 (with RP)
Coagulation Platelets x 10^3/mcL	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirrubin, mg/dL	< 1.2	1.2 – 1.9	2 – 5.9	6 – 11.9	> 12
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mmHg	Dop ≤ 5 or Dob at any dose	Dop > 5, Epi/Norepi ≤ 0.1	Dop > 15 Epi/Norepi > 0.1
Central Nervous System CGS	15	13 - 14	10 - 12	6 - 9	< 6
Renal Creatinine, mg/dL or Urine output mL/day	< 1.2	1.2 - 1.9	2 - 3.4	3.5 - 4.9 or < 500	> 5 or < 200

Table 3: *Sequential organ failure assessment (SOFA) score.*

PaO_2: Arterial Pressure of Oxygen; FiO_2: Inspired Fraction of Oxygen; RP: Respiratory Support; Dop: Dopamine; Dob: Dobutamine; Epi: Epinephrine; Norepi: Norepinephrine (the number is expressed in mcg/Kg/min); CGS: Coma Glasgow Scale.

It is important to note that a very recent retrospective study has shown that the combined SIRS + q-SOFA (q-SIRS) score is more accurate than q-SOFA alone in predicting mortality in patients with surgical sepsis in an ED [17].

While waiting for the results of the complete laboratory tests that will define the organ dysfunction, performing a blood gas test with lactate is a very simple, fast and helpful measure to stratify the severity, particularly among patients who scored 1 on q-SOFA the addition of a serum lactate level of 2 mmol/L (18 mg/dL) or higher identified those with a risk profile similar to those with 2 q-SOFA points [9].

As soon as we are aware the patient has low blood pressure (BP) (mean BP < 65 mmHg) and particularly if she/he has signs of hypoperfusion (determined by lactate greater than 2 mmol/L), a fluid challenge of at least 20 mL/kg of intravenous (IV) balanced crystalloids to target mean BP > 65 mmHg must be given within the first 3 hours, followed by subsequent fluid administration considering risks and benefits [18]. When this mean BP is not achieved with the fluid challenge, vasopressors should be implemented. At this point is highly recommended consulting to the ICU because the patient who needs vasopressors is, very likely, going to need a high number of personal resources within the following hours exceeding the standard nurse to patient ratio of the majority of the ED (Figure 1).

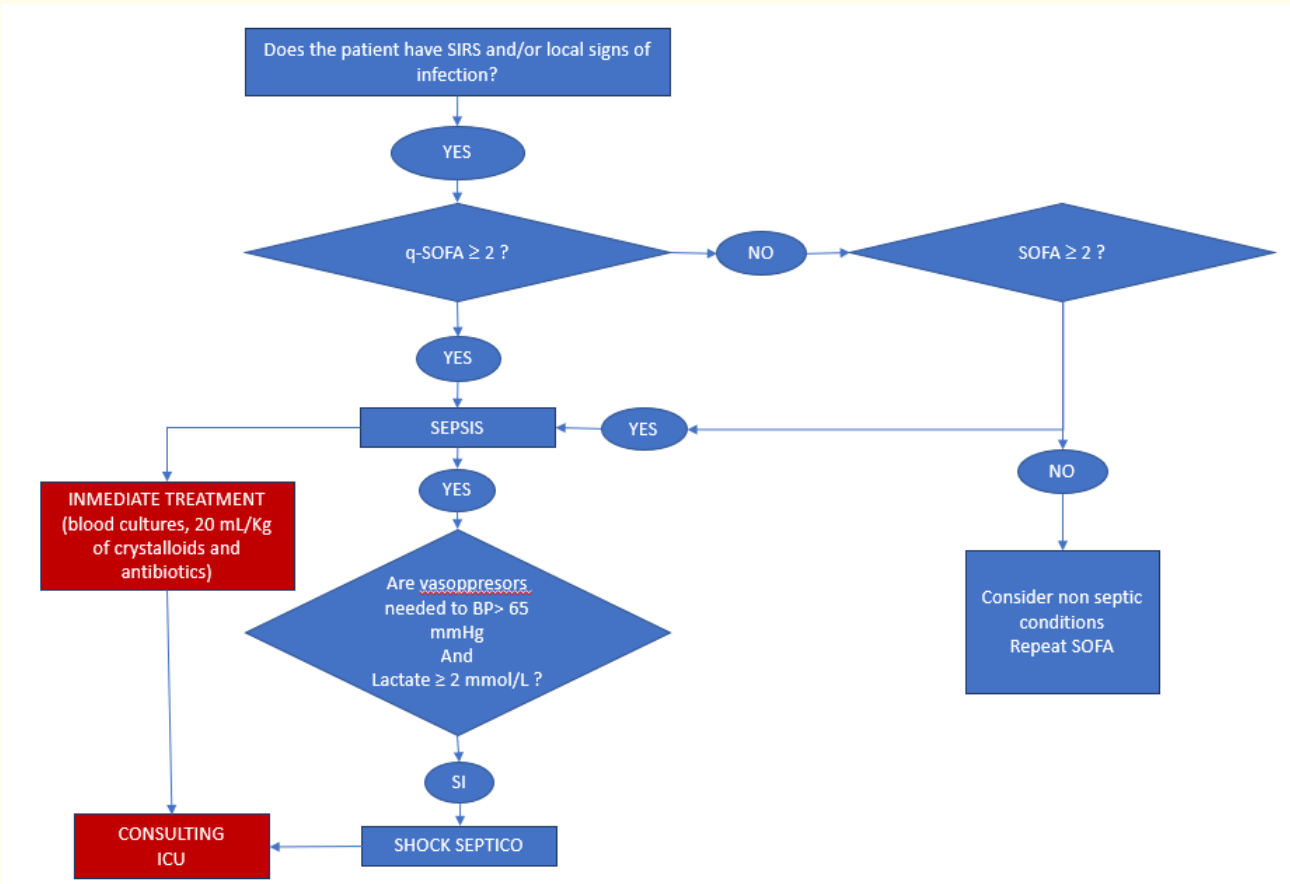

Figure 1: *Work flow to rule out sepsis and septic shock.*

In fact, according to the "Sepsis-3" definitions septic shock is defined as hypotension requiring vasopressor therapy to maintain mean BP 65 mmHg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation [1], so the sooner we know the lactate level the better.

Investigating the cause of the infection: initiating antimicrobials

Isolating the microorganism causing sepsis is crucial because it allows to give the best antimicrobial at the best dosing regimen optimizing its pharmacokinetics/pharmacodynamics. We must obtain blood cultures prior to the administration of antimicrobials without delaying the antibiotic initiation. It is also highly recommended to take samples from those suspected sites of infection, particularly when they are very easy to obtain as the urine or the skin discharge when it is obvious [12].

Nevertheless, the first dose of the antimicrobial has to be empiric and based on the most likely source of infection and causing pathogen. Knowing the epidemiology and the resistance profile for the most common pathogens of the area the patient is living in and his particular risk factors for being colonized by multi-resistant microorganisms are key points to consider before choosing the best treatment [19]. Discussing all the particular circumstances for each scenario is out of the scope of this editorial but it is important to remind that the failure to initiate appropriate therapy in septic patients, particularly in those in shock, is associated with higher morbidity and mortality [7]. So, in order to be pragmatic, the initial selection of antimicrobial therapy must be broad enough to cover all likely pathogens, what means to start two or even three antimicrobials depending on special circumstances [20]. For instance, an elderly immunosuppressed patient living in a health care facility suffering from pneumonia might need three antimicrobials covering multi-resistant gram negative and gram positive microorganisms.

The recent development of rapid and automated identification, in different biological samples, of the sensitivity profile of the pathogen causing sepsis based on resistance gene amplification will represent a paradigm shift in empirical treatment because the doctor can be informed in a few hours if the gram-negative or gram-positive isolated from the site of infection is resistant to beta-lactamase or carbapenem inhibitors, for example, or if it is resistant to cloxacillin, respectively [21-24].

Controlling the source of infection

As important as initiating the antimicrobials as soon as sepsis is diagnosed is controlling the source of infection [25]. This is why point 1 of this editorial highlighted the importance of identifying the specific anatomical site of infection [16].

When the patient suffers from pneumonia a chest ultrasound may help diagnose a potential empyema that should be drained. Consulting surgeons is mandatory when the abdomen is involved in order to remove or drain infected foci and to the urologist when an obstructive uropathy is suspected [26,27].

The skin and soft tissue infection might require extensive and prompt debridement, especially when necrotizing fasciitis appears. Sequential debridement should be done within the first 24 hours of treatment in most severe cases, particularly when group A *Streptococcus* (GAS) is involved and adding immunoglobulins to antibiotics may be considered in some cases [28].

Should not forget to remove the central line, if there is, when any other source of infection has been ruled out, particularly when the central line has been in place for a long time.

Supportive measures

Implementing concomitant therapies to support the failing organs as soon as they are needed is vital, particularly in cases of respiratory or renal failure. At this point the patient must be in an ICU.

The respiratory failure is one of the first life threatening scenarios that must be rapidly reversed in order to keep the patient alive. Administering oxygen is essential to improve hypoxemia as soon as it has been identified with a target oxygen saturation on pulse oximeter higher than 90%. The new high flow oxygen devices and noninvasive mechanical ventilation (NIMV) strategies [29] are particularly useful for those patients keeping a good level of consciousness with minor hemodynamic compromise but implementing invasive mechanical ventilation (IMV) under sedation should not be delayed, especially when the patient develops either encephalopathy or profound shock.

The renal dysfunction is quite common in cases of septic shock improving very often after fluid resuscitation. Nevertheless, when renal failure persists, initiating renal replacement therapy (RRT) might be necessary. Although the outcome seems to be quite similar independently of the timing the RRT is implemented [30], some patients become anuric and develop profound lactic acidosis and hyperkalemia very quickly. These patients might benefit from early continuous RRT, independently of their levels of creatinine, to control their fluid balance and acid-base equilibrium [31].

Other therapies such as low doses of corticosteroids are controversial but in cases of refractory shock after fluid resuscitation and dependence on high dose of noradrenaline the risk/benefit ratio might favor administering IV hydrocortisone at a dose of 200 mg/day because of its safety profile and potential to reverse shock [32], although might have no impact on the outcome. Of course steroids are indicated when there is a previous history of steroid therapy or adrenal dysfunction.

Conclusion

Every physician must be very systematic to diagnose the infected patient. Looking for the SIRS criteria, blood pressure and the site of infection is the first step. As soon as the infection seems likely, stratification of severity by q-SOFA at the ED and SOFA, even when the q-SOFA is low, should be calculated. While laboratory tests are available, performing a blood gas test with lactate is very helpful. When lactate is greater than 2 mmol/L and mean BP < 65 mmHg, blood cultures must be taken and 20 mL/Kg of crystalloids should be initiated. Antimicrobial treatment must be given taking into account the site of infection and the patient´s particular risk factors. Consulting the ICU is mandatory when organ dysfunction has been confirmed and particularly if the patient needs vasopressors. Additional measures may be necessary to control the source of infection. Oxygen administration and ventilatory support must not be delayed if the patient is hypoxemic.

Bibliography

1. Shankar-Hari M., *et al*. "Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)". *Journal of the American Medicine Association* 315.8 (2016): 775-787.

2. Bouza C., *et al*. "Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011)". *BMC Infectious Diseases* 14 (2014): 3863.

3. Angus DC and van der Poll T. "Severe sepsis and septic shock". *The New England Journal of Medicine* 369.21 (2013): 2063.

4. Wang HE., *et al*. "Revised National Estimates of Emergency Department Visits for Sepsis in the United States". *Critical Care Medicine* 45.9 (2017): 1443-1449.

5. Gaieski DF., *et al*. "Benchmarking the incidence and mortality of severe sepsis in the United States". *Critical Care Medicine* 41.5 (2013): 1167-1174.

6. Husabø G., *et al*. "Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: An observational study". *PLoS One* 15.1 (2020): e0227652.

7. Kumar A., *et al*. "Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock". *Critical Care Medicine* 34.6 (2006): 1589-1596.

8. Falcone M., *et al*. "Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*". *Critical Care Medicine* 24.1 (2020): 29.

9. Seymour CW., *et al*. "Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)". *Journal of the American Medicine Association* 315.8 (2016): 762-774.

10. Maitra S., *et al*. "Accuracy of quick Sequential Organ Failure Assessment (qSOFA) score and systemic inflammatory response syndrome (SIRS) criteria for predicting mortality in hospitalized patients with suspected infection: a meta-analysis of observational studies". *Clinical Microbiology and Infection* 24.11 (2018): 1123-1129.

11. Rhee C., *et al*. "Variation in Identifying Sepsis and Organ Dysfunction Using Administrative Versus Electronic Clinical Data and Impact on Hospital Outcome Comparisons". *Critical Care Medicine* 47.4 (2019): 493-500.

12. Rhodes A., *et al*. "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016". *Critical Care Medicine* 45.3 (2017): 486-552.

13. Singer M., *et al*. "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)". *Journal of the American Medicine Association* 315.8 (2016): 801-810.

14. Bone RC., *et al*. "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine". *Chest* 101.6 (1992): 1644-1655.

15. Abe T., *et al*. "In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission". *Critical Care* 23.1 (2019): 202.

16. Oliver ZP and Perkins J. "Source Identification and Source Control". *Emergency Medicine Clinics of North America* 35.1 (2017): 43-58.

17. Green SL., *et al*. "The Combined SIRS + qSOFA (qSIRS) Score is More Accurate Than qSOFA Alone in Predicting Mortality in Patients with Surgical Sepsis in an LMIC Emergency Department". *World Journal of Surgery* 44.1 (2020): 21-29.

18. Brown RM and Semler MW. "Fluid Management in Sepsis". *Journal of Intensive Care Medicine* 34.5 (2019): 364-373.

19. Kumar A. "Optimizing antimicrobial therapy in sepsis and septic shock". *Critical Care Clinics* 25.4 (2009): 733-751.

20. Martínez-Sagasti F., *et al*. "[Monotherapy vs. combined therapy in the treatment of multi-drug resistance gramnegative bacteria]". *Revista Española de Quimioterapia* 29.1 (2016): 43-46.

21. Tassinari M., *et al*. "Rapid diagnosis of bloodstream infections in the critically ill: Evaluation of the broad-range PCR/ESI-MS technology". *PLoS One* 13.5 (2018): e0197436.

22. Nieman AE., *et al*. "A prospective multicenter evaluation of direct molecular detection of blood stream infection from a clinical perspective". *BMC Infectious Diseases* 16 (2016): 314.

23. Trevino SE., *et al*. "Rapid MRSA PCR on respiratory specimens from ventilated patients with suspected pneumonia: a tool to facilitate antimicrobial stewardship". *European Journal of Clinical Microbiology and Infectious Diseases* 36.5 (2017): 879-885.

Citation: Fernando Martinez-Sagasti. "Five Key Points to Consider from a Practice Point of View when Sepsis is Suspected: A Pragmatic Approach for the First Six Hours". *EC Pharmacology and Toxicology* 8.3 (2020): 01-08.

24. Buehler SS., *et al*. "Effectiveness of Practices to Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis". *Clinical Microbiology Reviews* 29.1 (2016): 59-103.

25. Lagunes L., *et al*. "Current understanding in source control management in septic shock patients: a review". *Annals of Translational Medicine* 4.17 (2016): 330.

26. Sartelli M. "Evaluation and management of abdominal sepsis". *Current Opinion in Critical Care* (2020).

27. Dreger NM., *et al*. "Urosepsis--Etiology, Diagnosis, and Treatment". *Deutsches Aerzteblatt International* 112.49 (2015): 837-848.

28. Peetermans M., *et al*. "Necrotizing skin and soft-tissue infections in the intensive care unit". *Clinical Microbiology and Infection* 26.1 (2020): 8-17.

29. Vanoni NM., *et al*. "Management of Acute Respiratory Failure Due to Community-Acquired Pneumonia: A Systematic Review". *Medical Sciences* 7.1 (2019).

30. Barbar SD., *et al*. "Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis". *The New England Journal of Medicine* 379.15 (2018): 1431-1442.

31. Hoste EA and Dhondt A. "Clinical review: use of renal replacement therapies in special groups of ICU patients". *Critical Care* 16.1 (2012): 201.

32. Venkatesh B., *et al*. "Adjunctive Glucocorticoid Therapy in Patients with Septic Shock". *The New England Journal of Medicine* 378.9 (2018): 797-808.

Volume 8 Issue 3 March 2020