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Management of Sepsis in an Emergency Department in Italy in the Era of New Diagnostic Criteria: Are we Ready to Tackle this Rising Problem?

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Abstract

The early recognition of the septic patient has a pivotal role in sepsis management and it allows performing timely treatments and thus improving survival. The new guidelines of the SSC of 2016 (Sepsis-3) leave haemodynamic management schemes favouring simple protocols based on clinical judgment. This choice caused a wide debate, still ongoing, on the validity of the new criteria in terms of sensitivity and specificity, when compared to the previous one.

The purpose of this work is to analyse the clinical presentation of sepsis cases and their medical management in the ED of the University Hospital of Pisa, in Italy. The performance of the new diagnostic criteria for sepsis, compared to the previous ones, is also evaluated.

Our data show that in the ED to identify the septic patient, the clinical reasoning remains the most important element for diagnosing sepsis along with clinical manifestations.

SOFA score is a good tool to identify patients at risk of sepsis. The use of qSOFA alone must be re-dimensioned in identifying the septic patient, as specific but not sensitive. The values of lactates and PCT are helpful to the clinicians, also in ED.

High lactate values, qSOFA and the presence of septic shock, according to Sepsis-3, predict a greater probability of mortality for sepsis and therefore should direct patients in an intensive or sub-intensive setting.

Keywords: SOFA score; Lactate; qSOFA; Procalcitonin; Sepsis; Septic shock; SIRS; Surviving Sepsis Campaign

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease; CVC: Central Venous Catheter; ED: Emergency Department; GCS: Glasgow Coma Scale; ICD-9: Codes for International Statistical Classification of Diseases and Related Health Problems; ICU: Intensive Care Unit; NPV: Negative Predictive Value; PCT: Procalcitonin; PPV: Positive Predictive Value; qSOFA: Quick Sequential Organ Failure Assessment; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment; SSC: Surviving Sepsis Campaign; WBC: White Blood Cells

Introduction

Sepsis is an acute and rapidly evolving disease if not properly and promptly treated. The estimated global incidence exceeds 270 cases per 100,000 inhabitants/year with more than 2 million cases of sepsis per year and a mortality rate ranging between 20 and 40% [1].

As its incidence is continuously increasing worldwide, sepsis will increasingly affect the health

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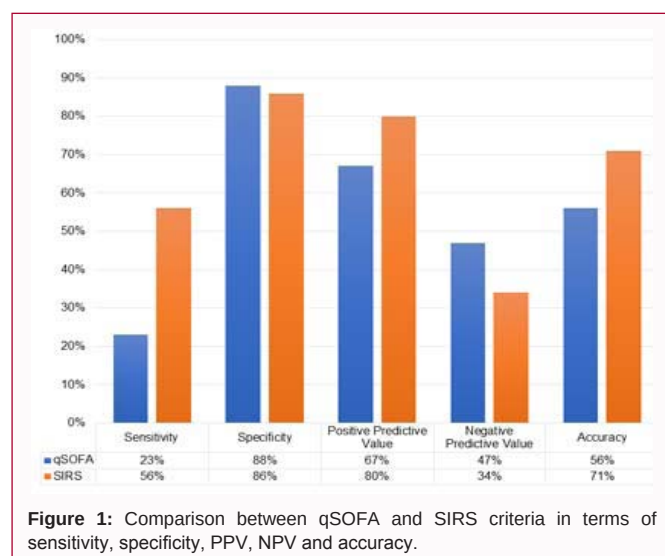
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care system and its proper management is necessary since the arrival of patients in the Emergency Department (ED).

Since 2001, Rivers shows the benefit in implementing an early management protocol of sepsis in the Emergency Department [2], an approach strongly recommend also in the different versions of the Surviving Sepsis Campaign (SSC) guidelines [3]. In fact, application of protocols for early recognition and management of sepsis in ED, as well as early antimicrobial therapy, remain essential actions to significantly reduce sepsis-related mortality [4,5].

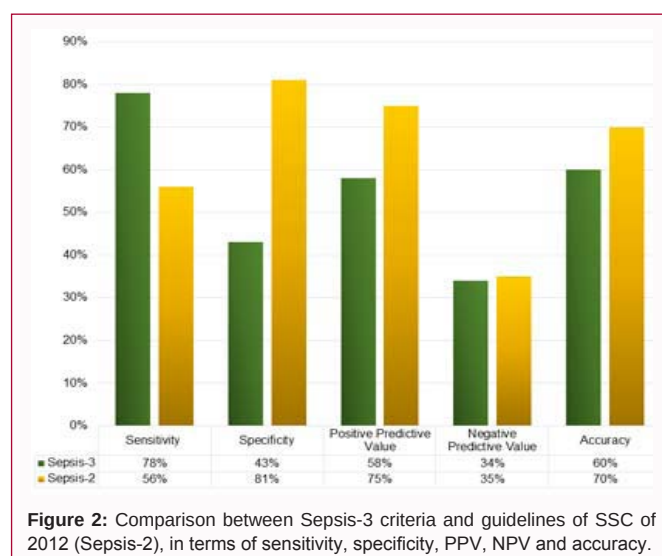
In 2016 a new definition of sepsis has been proposed, which remove the SIRS criteria, suggesting the SOFA score for diagnosis and the qSOFA for the early recognition of cases. The new guidelines of the SSC of 2016 (Sepsis- 3) leave previous haemodynamic management schemes favouring simple protocols based on clinical judgment. This choice caused a wide debate, still ongoing, on the validity of new criteria in terms of sensitivity and specificity.

The purpose of this work, whose data collection is still ongoing, is to analyse the clinical presentation of sepsis cases and their medical management in the ED of the University Hospital of Pisa, in Italy. The performance of the new diagnostic criteria for sepsis, compared to the previous ones, is also evaluated.

Materials and Methods

In this prospective case-control study, are enrolled septic patients who enter to the ED of Pisa Hospital from 1 March 2017 to 31 May 2017? Data collection is still ongoing and the work presented is a preliminary analysis. Cases are identified through the ICD-9 codes and discharge diagnosis of sepsis, severe sepsis or septic shock (n=139). Controls are enrolled for identical triage diagnosis in ED without discharge diagnosis of sepsis, severe sepsis or septic shock (n=138).

For each group (cases and controls) were investigated: demographic data, comorbidities and risk factors, clinical manifestations, blood tests, pharmacological therapies, duration of hospitalization and clinical outcome. In addition to the comparison between cases and controls, an analysis related only to mortality in infected group has been made. Finally, we estimated also the performances of SIRS, qSOFA, of the new definitions of sepsis and septic shock (Sepsis-3) comparing them with the previous SSC



definitions of 2012 (Sepsis-2).

Statistical analysis

Variables are described as median and interquartile range or proportion (depending on distribution). To compare variables, we used Mann-Whitney U test and Chi-square test. Chi-square test is used through Yates continuity correction or Fisher test, as required by the specific case. Normality of the variables was assessed with non-parametric Kolmogorov-Smirnov test. We used the statistical software SPSS for all statistical analyses and we consider a statistically significant p-value less than 0.05.

Results and Discussion

In this prospective case-control study, are enrolled patients 139 infected patients and 138 cases that enter to the ED of Pisa Hospital from 1 March 2017 to 31 May 2017?

Applying afterwards the new definitions (Sepsis-3) of sepsis and septic shock to the 139 infected cases results that 60 cases (43.16%) has should been diagnosed as sepsis and 51 cases (37.7%) as septic shock. Instead, physicians in ED recognized as sepsis only 39/139 cases (28%) and as septic shock only 7/139 cases (5%).

Respiratory infections were prevalent with 51/139 cases (36.7%), followed by urinary tract infections with 29/139 cases (20.1%).

The incidence of infected was higher in male than in female group (59.7% vs 40.3%). The median age in infected group was 78 years.

Among patient with infections: 113/139 patients (81.3%) received fluid-therapy with crystalloids, vasopressors were administered in 9/139 cases (6.5%), corticosteroids were administered as supportive therapy in 6/139 cases (4.3%), and 3/139 patients (2.15%) were transfused.

A set of blood cultures was collected in 56/139 septic patients (40.28%), and among these ones 36% was collected prior to the administration of empiric antibiotic therapy.

Empiric antibiotic therapy was administered in 86/139 cases (61.9%) and was a monotherapy in 36% of cases. We found that the most used antibiotics in ED in Pisa University Hospital were: piperacillin + tazobactam (49 cases, 57%); cephalosporins (25 cases, 29%); quinolones (12 cases, 14%); carbapenems (4 cases, 4%); glycopeptides (4 cases, 4%); macrolides (2 cases, 2%); cotrimoxazole

Table 1: Comparison between sepsis group and control group.

	Cases (n=139)	Controls (n=138)	p
Male gender	83 (59.7%)	46 (33.3%)	<0.001
Age	78 (67-85)	81.5 (73-88)	0.014
Charlsoncomorbidityindex	3 (1-4)	2 (1-4)	0.798
Cardiovascular diseases	72 (51.8%)	92 (66.7%)	0.012
Tumors	37 (26.6%)	34 (24.6%)	0.706
Diabetes	33 (23.7%)	36 (26.1%)	0.652
COPD	14 (10.1%)	29 (21%)	0.012
ChronicLiverdiseases	8 (5.8%)	3 (2.2%)	0.127
Oncoemathologydiseases	7 (5.0%)	2 (1.4%)	0.092
Renalfailure	3 (2.2%)	2(1.4%)	1
HIV	2 (1.4%)	0 (0%)	0.498
Chemioterapy or Radioterapy	14 (10.1%)	9 (6.5%)	0.284
Previous antimicrobial treatments (previous 30 days)	57 (41.3%)	7 (5.1%)	<0.001
Corticosteroidtreatments	22 (15.8%)	17 (12.3%)	0.401
Immunosuppressants	3 (2.2%)	3 (2.2%)	1
Previous trauma (previous 30 days)	10 (7.2%)	8 (5.8%)	0.637
Previous surgery (previous 30 days)	22 (15.8%)	7 (5.1%)	0.003
CVC	10 (7.2%)	0 (0%)	0.002
BladeCatheter	16 (11.5%)	4 (2.9%)	0.006
Intracardiac device	9 (6.5%)	12 (8.7%)	0.485
Osteo-articularprostheses	8 (5.8%)	6 (4.3%)	0.593
Vascularprostheses	5 (3.6%)	10 (7.2%)	0.18
Fever	50 (37.0%)	0 (0%)	<0.001
GCS	15 (14-15)	15 (15-15)	0.006
WBC (x10³)	13.3(10.2-20.1)	8.9(6.8-11.3)	<0.001
PCT (pg/ml)	1.18(0.44-6.52)	0.08(0.05-0.12)	<0.001
Lactatelevels>2 mmol/L	47 (34.8%)	22 (17.1%)	0.001
Lactatelevels>4 mmol/L	18 (14.4%)	5 (4.2%)	0.007
SOFA score	4 (2-5)	3 (2-4)	<0.001

(2 cases, 2%).

Results from a comparison between infected cases and controls are summarized in Table 1. It is possible to notice that in the control group there are more frequency of comorbidities such as cardiovascular diseases and COPD (respectively 66.7% vs. 51.8% and 21% vs. 10.1%). Patients with cardiovascular diseases and COPD arrive in ED with symptoms related to shock or respiratory failure, such as septic patients, and therefore frequently receive the same triage diagnosis. On the contrary, in the infected patients, emerge as risk factors for sepsis: previous antibiotic therapy (41.3% vs. 5.1%) and previous surgical procedures (15.8% vs. 5.1%), both evaluated in the previous 30 days, and the presence of device such as CVC (7.2% vs. 0%) and bladder catheters (11.5% vs. 2.9%). In addition, septic patients, compared with controls, are younger (median age 78 vs. 81.5 years) and more frequently male (59.7% vs. 33.3%). Among clinical manifestations of septic cases in ED, when compared to control group, we found the following statistically significant differences: a higher frequency of fever; a lightly reduced GCS; a higher value of WBC; a higher value of PCT and lactates. The SOFA score is also higher in septic group (Table 1).

Table 2: Comparison between 24 cases of death due sepsis, severe sepsis and septic shock and 115 surviving septic patients.

	Dead (n=24)	Survivors (n=115)	p
Length of stay (days)	3 (1-8)	7 (4-10)	0.003
Hospitalization in ICU	5/23 (21.7%)	9/113 (8.0%)	0.062
Age	80.5(69.5-87)	78 (67-85)	0.401
Charlson score index	3.5(2-5)	3(1-4)	0.079
Cardiovascular disease	18/24 (75.0%)	54/115 (46.9%)	0.012
Body temperature (°C)	36.9(36-37.7)	37.7 (36.8-38.4)	0.004
Lactate value (mmol/L)	2.9 (1.8-5.8)	1.2 (0.8-2.2)	<0.001
Lactate levels>2 mmol/L	15/23 (65.2%)	33/112 (29.5%)	0.001
Lactate levels >4 mmol/L	8/23 (34.8%)	10/112 (8.9%)	0.003
PCT (pg/ml)	2.9 (0.72-9.43)	1.0 (0.38-5.36)	0.085
Administration of vasopressive amines	4/24 (16.6%)	5/115 (4.3%)	0.048
SOFA score	5 (4-7)	3 (2-4)	0.001
qSOFA prediction	10/24 (41.6%)	22/115 (19.0%)	0.017
SIRS	16/24 (66.7%)	62/115 (53.9%)	0.252
Sepsis (Sepsis-3)	5/24 (20.8%)	55/115 (47.8%)	0.015
Septic Shock (Sepsis-3)	17/24 (70.8%)	34/113 (30.0%)	<0.001
Sepsis and severe sepsis (Sepsis-2)	13/24 (54.2%)	57/115 (49.6%)	0.682
Septic Shock (Sepsis-2)	3/24 (12.5%)	4/115 (3.4%)	0.099

The overall mortality with sepsis and septic shock is estimated at 17% (24/139 patients). By comparing these 24/139 patients who died due to sepsis, severe sepsis and septic shock, with the surviving patients (115/139, 83%), we found the following statistical significance, summarized in Table 2. Higher mortality is found in those septic cases that show: a cardiovascular disease as comorbidity; a lower body temperature; a higher value lactates and SOFA score; have required use of amines in ED; have a positive qSOFA prediction and are identified from new diagnostic criteria for septic shock.

Starting from values of false positives, false negatives, true positives, and true negatives (Table 3), we compared sensitivity, specificity, PPV, NPV and accuracy of qSOFA vs. SIRS (Figure 1) and new Sepsis-3 criteria vs. previous Sepsis-2 (Figure 2).

From this data emerges that in ED are not always still performed the microbiological cultures and the appropriate antibiotic therapies in case of sepsis. Collecting microbiological cultures before administration of antibiotics increase the probability to isolate the microorganism responsible for sepsis; in fact, blood cultures can be sterilized if performed even minutes or hours after the administration of antimicrobials [6, 7]. Timely administration of appropriate antibiotic therapy after collecting blood cultures was essential for effective treatment and reduces mortality [5,8-10].

Our data show that an accurate anamnesis and clinical manifestations remain extremely important to identify the septic patient in ED. In fact, in front of a patient with previous surgeries or antibiotic therapies, biomedical devices, which presents fever or high leukocyte count or a reduced GCS, we must always think for a possibility of sepsis.

SOFA score is a good tool to identify patients at risk of sepsis, as is also considered in the new definitions of Sepsis-3 [11].

PCT is a diagnostic tool that allows patient identification,

Table 3: Values (and percentage) of false positives, false negatives, true positives, and true negatives of qSOFA, SIRS, Sepsis-3 criteria, Sepsis-2 criteria.

	qSOFA	SIRS	Sepsis-3	Sepsis-2
True Positive	32/139(23.0%)	78/139 (56.1%)	108/139 (77.7%)	78/139 (56.1%)
True Negative	122/138 (88.4%)	118/138 (85.5%)	59/138 (42.7%)	112/138 (81.2%)
False Positive	16/138 (11.6%)	20/138 (14.5%)	79/138 (57.2%)	26/138 (18.8%)
False Negative	107/139 (77.0%)	61/139 (43.9%)	31/139 (22.3%)	61/139 (62.7%)

treatment and risk stratification as well as support for antimicrobial stewardship and therapeutic de-escalation [12-14]. These data confirmed the role of PCT to better identify septic patients in ED.

About bedside lactate level, it is shown that a higher level than 2mmol/L was associated with a worse outcome in terms of mortality, ICU stay and need for vasopressor [15]. This studio showed as lactate levels are usually higher in septic groups and respecially in those septic patients who died for sepsis.

Scientific literature of recent years reports that SIRS criteria are sensitive but have limited ability to discriminate septic patients from those with a simple infection. Following Sepsis-3, several retrospective and meta-analysis are performed to compare qSOFA and SIRS, with non-conclusive results. Singer's work shows that qSOFA is useful in predicting mortality, ICU admission, and length of stay [11]. Freund et al show that qSOFA has better prognostic accuracy in terms of mortality when compared to SIRS and severe sepsis [16]. Askim et al show that qSOFA has failed to identify 2 out of 3 septic patients and that qSOFA sensitivity is worse than SIRS parameters [17]. Serafim's work concludes that the SIRS criteria are more sensitive than qSOFA for the diagnosis of sepsis, while qSOFA is able to better predict mortality. Juffroy et al compare the performance of SIRS and qSOFA in identifying septic patients: despite qSOFA being more specific and not very sensitive, the PPV and NPV are similar [18].

In our study the difference in sensitivity between these two scores is confirmed, however the specificity is similar (qSOFA: 88%, SIRS: 86%), the PPV is higher for SIRS and the NPV is higher for qSOFA. Overall, the SIRS criteria show greater accuracy.

In our study new definitions of sepsis and septic shock (Sepsis-3) show a greater sensitivity but a lower specificity than the previous ones (Sepsis-2). Overall accuracy is higher for Sepsis-2 than Sepsis-3. The new definitions of sepsis and septic shock (Sepsis-3) should have a better ability to identify patients with higher risk of mortality than previous versions (Sepsis-2). Among patients who died, septic shock according to the 2016 definitions and qSOFA identified better cases with a worse outcome. From these data we can deduce that the new definitions (Sepsis-3) identify the most critical patients better but may not take into consideration those patients who had less predictable clinical manifestations. The previous definitions (Sepsis-2), including more clinical manifestations and a greater number of parameters, helped to identify patients with minor clinical manifestations.

Conclusion

The early recognition of the septic patient is a pivotal of sepsis management as it allows performing timely treatments and thus improving survival. But, in conclusion, there are currently insufficient data to give definitive indications on the method to be used for early identify a septic patient in ED.

In the ED to identify the septic patient, the clinical reasoning,

which considers for example an accurate anamnesis to identify risk factors such as CVC, bladder catheter, previous antibiotic therapies or surgical interventions, remains the most important element for diagnosing sepsis along with clinical manifestations.

SOFA score is a good tool to identify patients at risk of sepsis. The use of qSOFA alone must be evaluated in identifying the septic patient, as specific but not sensitive. The values of lactates and PCT are helpful to the clinicians, also in ED.

High lactate values, qSOFA and the presence of septic shock according to Sepsis-3 predict a greater probability of mortality for sepsis and therefore should direct patients in an intensive or sub-intensive setting.

An effort should be made to know local epidemiology of infections from the ED, in order to create local protocols of empiric therapy based on epidemiology. Collecting microbiological cultures before empiric antibiotic therapy is very important, both to define the local epidemiology and to perform a targeted therapy.

Disclosures

C.T. has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck and Astellas. All other authors: none to declare.

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