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Accuracy of point of care ultrasound to identify the source of infection in septic patients: a prospective study

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Abstract Sepsis is a rapidly evolving disease with a high mortality rate. The early identification of sepsis and the implementation of early evidence-based therapies have been recognized to improve outcome and decrease sepsis-related mortality. The aim of this study was to compare the accuracy of the standard diagnostic work-up of septic patients with an integrated approach using early point of care ultrasound (POCUS) to identify the source of infection and to speed up the time to diagnosis. We enrolled a consecutive sample of adult patients admitted to the ED who met the Surviving Sepsis Campaign (SSC) criteria for sepsis. For every patient, the emergency physician was asked to identify the septic source after the initial clinical assessment and after POCUS. Patients were then addressed to the standard predefined work-up. The impression at the initial clinical assessment and POCUS-implemented diagnosis was compared with the final diagnosis of the septic source, determined by independent review of the entire medical record after discharge. Two hundred consecutive patients entered the study. A final diagnosis of the septic source was obtained in 178 out of 200 patients (89 %). POCUS-implemented diagnosis had a sensitivity of 73 % (95 % CI 66–79 %), a specificity of 95 % (95 % CI 77–99 %), and an accuracy of 75 %. Clinical impression after the initial clinical assessment (T0) had a sensitivity of 48 % (CI 95 % 41–55 %) and a specificity of 86 % (CI 95 % 66–95 %). POCUS improved the sensitivity of the initial clinical impression by 25 %. POCUS-implemented diagnoses were always obtained within 10 min. Instead the septic source was identified within 1 h in only 21.9 % and within 3 h in 52.8 % with a standard work-up. POCUS-implemented diagnosis is an effective and reliable tool for the identification of septic source, and it is superior to the initial clinical evaluation alone. It is likely that a wider use of POCUS in an emergency setting will allow a faster diagnosis of the septic source, leading to more appropriate and prompt antimicrobial therapy and source control strategies.

Keywords Sepsis · Septic shock · Early diagnosis · Ultrasound imaging · Critically ill · Accuracy

Introduction

Sepsis is a rapidly evolving disease associated with a high mortality rate [1]. Most patients meet the criteria for severe sepsis on the same day that they meet the criteria for sepsis or develop septic shock on the same day of severe sepsis [2]. The early identification of sepsis and the implementation of early evidence-based therapies have been recognized to improve outcome and decrease sepsis-related mortality [3, 4, 5]. In particular, there is evidence that the timing of initiation of effective antibiotic treatment in septic shock strongly correlates with prognosis [6–11]. The SSC guidelines [12] recommend that an adequate antibiotic treatment be started within a maximum of 3 h from the initial patient evaluation, and that the septic source removal be achieved within 12 h. Unfortunately, time to complete imaging in the emergency department (ED) may delay the identification of the septic source in many patients [13–15].

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In this context, a rapid bedside method to identify the septic source could speed up the diagnosis, thus favoring early and appropriate therapeutic interventions [16, 17]. POCUS may be effective in identifying septic source from pleuro-pulmonary, abdominal, soft tissue, and cardiac origin.

Since the value of using early POCUS to identify the source of infection has not been fully investigated, we designed a study with the primary aim of evaluation of the diagnostic accuracy of a POCUS-implemented approach compared with the final diagnosis. As the secondary outcome, we evaluated the time to septic source identification with the POCUS-implemented approach and with a standard work-up.

Methods

The study was performed at the ED of a tertiary care teaching hospital (Grande Ospedale Metropolitano Niguarda, Milan, Italy) between April 2015 and September 2015. The study was approved by the local and Regional Ethics Committee, and all patients gave an informed written consent to participate in the study (see Appendix 1).

Patients

We conducted a single-centre, prospective trial involving a cohort of consecutive adult patients admitted to the ED who met the SSC criteria for sepsis [12]: the presence (probable or documented) of infection together with two or more systemic manifestations of infection, as reported in Appendix 2. Exclusion criteria were refusal to participate or the impossibility of obtaining a signed informed consent.

Study protocol

After the initial clinical assessment (history, physical examination, arterial blood gases, and lactate), a provisional diagnosis of the septic source, a diagnostic work-up, and therapeutic interventions were recorded by the physician (Clinical impression, T0). Within 10 min after the initial clinical assessment, the same physician performed POCUS, and, immediately after that, a "POCUS-implemented diagnosis" (T1) was recorded. Possible changes in antimicrobial therapy were also recorded. Patients were subsequently addressed by the standard work-up initially established after clinical T0 and before POCUS evaluation (including laboratory tests and the whole diagnostic imaging work-up interpreted by a radiologist). Information obtained by POCUS did not change the scheduled diagnostic work-up, but on an ethical basis, POCUS was allowed to change the therapeutic pathway established at T0.

After hospital discharge, two emergency physicians, blinded to POCUS results and experienced in sepsis (reference physicians for sepsis training protocols), independently reviewed the entire medical records of patients (imaging, laboratory, and hospital course) and indicated the source of patient's sepsis. In the case of disagreement, a third expert emergency physician reviewed the medical records for the clinical diagnosis that was finally recorded (T2).

POCUS

All POCUS examinations were performed bedside, with a portable machine with sector (2–2.5 MHz), convex (3.5–5 MHz) and linear probes (5–7) (Esaote®, 30 Gold—Medical System, Firenze, Italy). After the initial clinical assessment, lung, abdominal, cardiac, joint or soft tissue organs were examined in consideration of symptoms and of the initial diagnostic impression (see Appendix 3). In the absence of a clear clinical diagnosis, POCUS was performed at all the above-mentioned anatomical sites [20, 21].

All doubtful results obtained with POCUS examination were considered as non-diagnostic as recommended in the literature [22].

POCUS was performed by emergency physicians trained according to the Italian Society of Emergency Medicine [SIMEU] guidelines with SIMEU and WINFOCUS certification in emergency ultrasound; POCUS-trained physicians on duty were equally distributed during night, day, and week end to avoid any selection bias.

Statistics

The final diagnosis (T2) was considered as the standard reference to calculate sensitivity, specificity, and accuracy of the POCUS-implemented approach, and all parameters were calculated using the standard 2×2 contingency tables for definitive final clinical diagnosis. Student's t test was used for continuous variables, while the t^2 test or McNemar test was used for dichotomous variables when appropriate [23].

Results

Two hundred consecutive patients were enrolled. Mean age was 64.2 years (min 19, max 102, standard deviation ± 18), 53.7 % of the population were male, and 71/200 patients (35 %) met diagnostic criteria for severe sepsis or septic shock.

A septic source was identified in 178/200 patients (89 %), while 22 patients (11 %) received a final diagnosis of sepsis of undetermined origin. The most prevalent source of infection was pneumonia (39.5 %), followed by urinary tract and abdominal infections (23 and 19.5 %, respectively) (Table 1). The standard work-up identified a septic source within 1 h in 21.9 % of the population (39/178), within 3 h in 52.8 % (94/178), and within 6 h in 71.3 %. In 15.7 % of the population (28/178), septic source identification took longer than 24 h (Fig. 1).

POCUS-implemented diagnosis (T1) identified 130/178 septic sources with a sensitivity of 73 % (95 % CI 66–79 %). Among the 48 sources not immediately identified by POCUS, 30 were urinary tract infections (UTI).

POCUS was false positive in one patient (in whom a soft tissue abscess was considered the septic source before a final diagnosis of malaria could be made) with a specificity of 95 % (95 % CI 77–99 %).

Accuracy of POCUS was 75 %. Positive Likelihood ratio was 16.06 (IC 95 % 2.36–109), and negative likelihood ratio was 0.28 (IC 95 % 0.21–0.36) (Table 2). All the POCUS-implemented diagnoses were obtained within 10 min.

The sensitivity of POCUS-implemented diagnoses had different values depending on the septic source being higher for pneumonia and abdominal infections. More specific evaluations about other district are biased by the low statistical power because of the small sample size (Table 3).

Table 1 Identified septic sources

	No.	%
Respiratory infections	79	39.5
Pneumonia	79	39.5
Abdominal infections	39	19.5
Cholecystitis	13	6.5
Cholangitis	11	5.5
Appendicitis	6	3.0
Diverticulitis	6	3.0
Intra-abdominal abscesses	3	1.5
Urosepsis	46	23.0
Urinary tract infections (UTI)	29	14.5
Hydronephrosis/Pyelonephritis	17	8.5
Endocarditis	2	1.0
Joint abscesses	1	0.5
Musculoskeletal abscesses	2	1.0
Hepatic abscesses	1	0.5
Meningitis	2	1.0
Other	6	3.0
Total identified	178	89.0
Unidentified septic source	22	11.0
Total	200	100.0

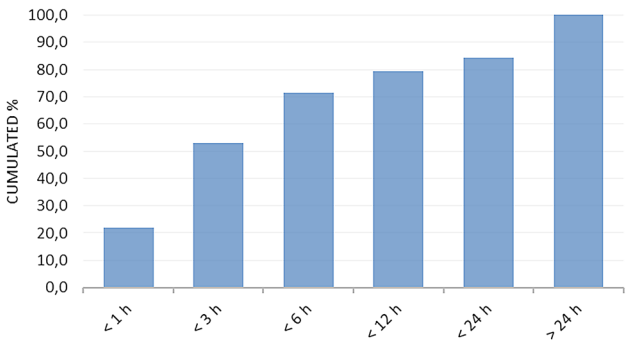

Fig. 1 Time to diagnosis with the standard work-up. Cumulative percentage of identified diagnosis grouped by time intervals

When clinical impression after the initial clinical assessment (T0) was compared with the final diagnosis (T2), it had a sensitivity of 48 % (CI 95 % 41–55 %), with 86/178 diagnoses identified, and a specificity of 86 % (CI 95 % 66–95 %) with 3/22 false positive results. Positive likelihood ratio was 3.54 (CI 95 % 1.22–10.25), and negative likelihood ratio was 0.59 (CI 95 % 0.48–0.74).

Accuracy of the diagnosis after the clinical impression was 52.5 %. POCUS improved by 22.5 % the accuracy of the initial clinical diagnosis, and this result was statistically significant with Mc Nemar test ($p < 0.001$), showing a marked improvement when compared with the clinical impression alone (Fig. 2).

Discussion

In this study, we investigated the role of POCUS for early identification of the source of infection in septic patients accessing the ED. The role of emergency ultrasound for the differential diagnosis of non-traumatic, undifferentiated hypotension (mostly prevalent in septic patients) has already been documented [24].

At the end of a complete work-up, we identified the septic source in 89 % of enrolled patients, a finding in agreement with other reported data [25]. The sensitivity of POCUS was greater than 90 % for pneumonia, almost 80 % for soft tissue infection and cholecystitis, and about 60 % for diverticulitis and appendicitis. These results are in accordance with other reported data [18], with the exception of a slight inferiority in the detection of abdominal infection, where a sensitivity between 70 and 90 % has been reported by other authors [19].

POCUS may not identify the source of infection such as with a urinary tract infection, where the diagnosis is usually based on a careful history and physical examination and on the analysis of a urine sample. However, POCUS is

Table 2 Sensitivity and specificity of POCUS diagnosis vs final diagnosis (standard reference)

	Final diagnosis POS[a] (*n*, %)	Final diagnosis NEG[b] (*n*, %)	Tot.
POCUS POS[c] (*n*, %)	130 (73 %)	1 (4 %)	131
POCUS NEG[d] (*n*, %)	48 (27 %)	21 (96 %)	69
Tot.	178	22	200

[a] Identified final diagnosis at t2

[b] Unidentified final diagnosis at t2

[c] Identified POCUS diagnosis at t1

[d] Unidentified POCUS diagnosis at t1

Table 3 Sensitivity of POCUS diagnosis vs final diagnosis (standard reference) grouped by anatomic district

Anatomic district	Sens ± SD	95 % CI
Respiratory infections	0.97 ± 0.03	0.93–1.00
Abdominal infections	0.79 ± 0.13	0.67–0.92
Urosepsis	0.33 ± 0.14	0.19–0.46
Endocarditis[a]	0.50 ± 0.69	0.00–1.00
Joint abscesses[a]	1.00 ± 0.00	1.00–1.00
Musculoskeletal abscesses[a]	1.00 ± 0.00	1.00–1.00
Other	0.33 ± 0.31	0.03–0.64

Sens sensitivity, *SD* standard deviation, *CI* confidence interval

[a] Inadequate sub-sample size

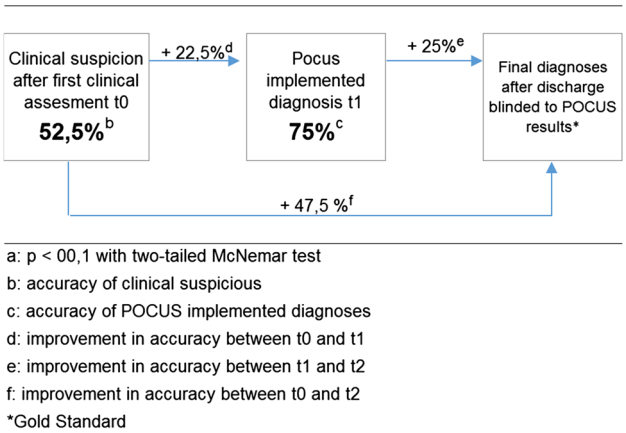

Fig. 2 POCUS accuracy improvements. *t0* clinical suspicion after first clinical assessment, *t1* POCUS (point of care ultrasound)-implemented diagnoses, *t2* final diagnoses after discharge performed by two physicians blinded to POCUS results

very valuable for quickly ruling out other sources of infection. The elimination of some of the potential differential diagnoses allows the physicians to focus their diagnostic evaluation, increasing accuracy in diagnosis and treatment in a very short time. The standard work-up required longer than 6 h to confirm the site of infection in more than 30 % of patients.

In our study, antimicrobial therapy indicated as the physician's choice after the initial clinical work-up was changed after POCUS in about a quarter of patients (24 %), and it was always in accordance with the final diagnosis except in one case of POCUS false positive result of soft tissue abscess as the septic source, with a final diagnosis of malaria. POCUS was also able to identify rarer causes of infection, such as endocarditis or intra-abdominal abscesses.

Another clear advantage of POCUS was its ability to quickly identify the need for a source control strategy [10, 12] in about 20 % of cases: 44 patients underwent surgery or interventional radiology for hydronephrosis with ureterolithiasis, or endoscopic procedures in cholangitis with biliary obstruction.

Finally, the high specificity of POCUS may help prevent needless antimicrobial therapy for those patients who do not have any infection as may happen for community acquired pneumonia (CAP), where about 17 % of hospitalized patients with CAP were proved not to have an infection as a final diagnosis [26].

Limitations

Our study has several limitations: first, it is a monocentric non-randomized study. Methodologically, it would have been more correct perform a randomized trial (as Jones et al. in their study on goal-directed ultrasound in non-traumatic hypotension [25]), but we considered this methodology not ethical in our reality, where all emergency physicians use POCUS as a standard complemental support of clinical evaluation of critical patients.

The second limitation is that POCUS findings might be biased by the information derived from history and physical examination, since the same physician approached the patient, decided the diagnostic work-up, and then performed POCUS. However, the diagnostic work-up in our POCUS protocol could not be changed after decision during T0 first clinical assessment. A third limitation in our study is that reproducibility may be limited, as the study physicians had fairly advanced levels of point of care ultrasound skills, including ability to identify diverticulitis or appendicitis. Finally, our study lacked the power to investigate the impact of POCUS-implemented diagnosis on mortality in septic patients.

Conclusions

Bedside POCUS is a reliable diagnostic tool to identify a septic source, and can increase the accuracy of the initial clinical evaluation. It is likely that a wider use of POCUS will help physicians to obtain a faster diagnosis of the site of infection, thus allowing a more appropriate antimicrobial therapy and the prompter activation of a control strategy of the septic source.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix 1. Informed consent to participate

MODULO DI CONSENSO INFORMATO

Io sottoscritto/a _____

nato/a_____il_____

dichiaro di essere stato informato in modo esauriente sugli obiettivi e le caratteristiche

dello studio "L'Accuratezza dell'ecografia clinica precoce nell'identificare la fonte settica nel dipartimento d'Emergenza-Urgenza"

dal Dr./Dr.ssa_____

Confermo di aver ricevuto e letto il presente modulo e di aver avuto risposte esaurienti ai miei quesiti in merito.

Dichiaro inoltre, di essere a conoscenza della mia libera partecipazione allo studio e della possibilità di revocare il presente consenso in qualsiasi momento.

[ ] ACCONSENTO

Data_____ Firma del paziente_____

Firma del medico che ha ottenuto il consenso_____

Appendix 2. Surviving Sepsis Campaign criteria for sepsis

Criteri diagnostici per sepsi. Adapt. Ref. [27].

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° or < 35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Appendix 3. Technical approach of POCUS

Descriptive POCUS findings

Anatomic district	Normal findings	Pathological findings
Lung		
Anterolateral and posterior scans (two anterior, two lateral, one posterior)		
Convex 3.5–5 MHz probe/linear 5–7 mHz probe		
Sub-pleural lung consolidation, presenting a tissutal pattern with dynamic air or multiple hyper-echogenic spots	No	Yes
Focal interstitial syndrome	No	Yes
Presence of pleural fluid	No	Yes
Heart		
Parasternal view (long and short axis), apical view, subcostal view (4-chambers)		
Sector 2–2.5 MHz probe		
Presence of vegetation on the valve surface	No	Yes
Abdomen		
(1) Gallbladder and biliary duct		
Convex 3.5–5 MHz probe		
Wall thickness >4 mm	No	Yes
Pericholecystic fluid	No	Yes
Gallstones/sludge	No	Yes
Echographic murphy sign	No	Yes
Common bile duct >5 mm	No	Yes
(2) Liver		
Convex 3.5–5 MHz probe		
Hepatic abscess		
Ascites (primary PBS)	No	Yes
(3) Diverticula		
Convex 3.5–5 MHz probe/linear 5–7 mHz probe		
Presence of diverticula	No	Yes
Wall thickness >3 mm	No	Yes
Inflammatory peri-colonic fat	No	Yes
Presence of abscesses	No	Yes
Peri-colonic free fluid	No	Yes
(4) Appendix		
Convex 3.5–5 MHz probe/linear 5–7 mHz probe		
Total diameter on cross section >6 mm or Wall thickness >3 mm		
Non compressible-appendix	No	Yes
Inflammatory peri-appendiceal fat	No	Yes
Presence of abscesses	No	Yes
Peri-appendiceal free fluid	No	Yes
(5) Abdominal-muscle abscesses		
Convex 3.5–5 MHz probe		
Presence of abscesses	No	Yes
(6) Kidney		
Convex 3.5–5 MHz probe		
Hydronephrosis	No	Yes
Presence of renal abscess	No	Yes
Urethorolithyasis	No	Yes
Joints		
Linear 5–7 mHz probe		
Intra-articular fluid	No	Yes

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