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SEPSIS AND SIRS:
A FOCUS ON ECHOCARDIOGRAPHY IN CLINICAL SETTING

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ABSTRACT

The present narrative review aims to focus on the diagnostic process in case of patient with SIRS (systemic inflammatory response syndrome) or sepsis confirming or ruling out concomitant diagnosis of infectious endocarditis.
We focused on the proper indications for both transthoracic and transoesophageal echocardiography in SIRS/septic patients, reviewing the scientific literature and the updated international guidelines on the topics.
We suggest a flow chart tool to assist during the diagnostic process of infectious endocarditis, including an adequate use of echocardiography.

BACKGROUND

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection"[(1)]. The prevalence of sepsis is about 1.3% among hospitalized people and in USA and in the last decades its incidence rate was 2.4 cases over 1000 persons, with an annual increase of 8.7% between 1979 and 2000[(5)].
Sepsis represents a clinical condition with a remarkable economic burden all over the world. Infectious endocarditis may be involved as ethiologic cause or consequence of septic status in septic patients.
The present narrative review aims to focus on the diagnostic process in case of patient with SIRS (systemic inflammatory response syndrome)[(2)] or sepsis confirming or ruling out concomitant diagnosis of infectious endocarditis.
We focused on the correct diagnostic process and stressed the proper indications for both transthoracic and transoesophageal echocardiography in SIRS/septic patients, reviewing the scientific literature and the updated international guidelines on the topics.
Moreover, we suggest a flow chart tool to assist during the diagnostic process of infectious endocarditis, including an adequate use of echocardiography.

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Keywords:
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METHODS

We reviewed the main scientific literature available about SIRS, sepsis and infectious endocarditis using Pubmed as a search database.
We used the following keywords: sepsis, SIRS, infectious endocarditis, echocardiography and we searched for correlations clinical and epidemiological between SIRS/sepsis and infectious endocarditis.
The "Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)"[1] statement, the modified Duke criteria papers[23] and the recently updated EACVI/ESC[31,32] guidelines were considered in this review as key documents , respectively for sepsis, infectious endocarditis diagnosis and use of echocardiography in infectious endocarditis diagnosis. All definitions, tables e pictures report data derived from the sources mentioned above.
The suggested diagnostic flow chart has to be considered as personally reviewed and re-built tool of some of the combined above data to assist in physicians daily practice.

EPIDEMIOLOGY

According to updated guidelines based on "Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)", sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection"[1].
Sepsis thus is considered a specific clinical condition that has to be differentiated from SIRS (Systemic inflammatory response syndrome)[2].

Criteria to make SIRS diagnosis are reported in (Table 1.)

TAB.1 DIAGNOSTIC CRITERIA FOR SIRS

Two or more of:	
Temperature	>38°C or <36°C
Heart rate	>90/min
Respiratory rate	>20/min or PaCO2 <32mmHg (4.3 kPa)
White blood cell count	>12 000/

Getting deeper in pathophysiologic knowledge of sepsis through years, specific clinical criteria has been identified to make a correct diagnosis. Sepsis is in fact a clinical condition that involves host response to an infecting pathogen: this response may be significantly amplified by endogenous factors. Furthermore, the diagnosis of sepsis necessarily involves organ dysfunction. The evaluation of organ dysfunction is aided by the current use of SOFA (Sequential Organ Failure Assessment) score in clinical practice. The SOFA score is reported in Table 2[3].

We could then briefly summarize the definition of sepsis as "suspected or documented infection and an acute increase by ≥2 of the SOFA score".
Furthermore the definition of "septic shock" has been developed. Septic shock is a subset of sepsis in which underlying circulatory and metabolic abnormalities imply dysregulation of vasoactive homeostasis lowering levels of mean arterial pressure and remarkably increasing mortality rate.
Septic shock is thus defined as "sepsis and vasopressor therapy needed to elevate MAP (mean arterial pressure) ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation"[4].
The prevalence of sepsis is remarkable: approximately accounting 1.3% of all hospitalizations, in USA in the last decades incidence of sepsis was set 2.4 cases over 1000 population with an annual increase of 8.7% between 1979 and 2000[5].
Epidemiological studies in Europe report similar overall data with mean mortality rates accounting for approximately 13,5% to 52%, increasing with age[5,6,7,8]. In 2011 sepsis accounted in USA for more than 20 billion dollars (5.2%) of total US hospital costs[9].
European datas show a remarkable increase in management costs of survived patients before and after sepsis hospitalization (including hospital care, pharmaceutical care, rehabilitation facilities, nursing homes, and home care, physical therapy, occupational therapy, speech therapy, dietetics, consultations of social workers, psychologists, and psychiatrists): unadjusted mean monthly health care cost per patient increased from €1,035 to €3,533 (crude cost difference €2,498; adjusted cost difference €2,281)[10].

TAB.2 SOFA (SEQUENTIAL ORGAN FAILURE ASSESSMENT) SCORE

	SCORE				
SYSTEM	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO2/FiO2 mmHg (kPa)	≥400 (53.3)	≥400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, x103/μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
	MAPa ≥70 mm Hg	MAPa <70 mm Hg	Dopamine <5 or dobutamine (any dose) μg/kg/min	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 μg/kg/min	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 μg/kg/min
Central nervous system					
GCSb score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)

[a]mean arterial pressure; [b]Glasgow Coma Scale

The clinical condition of sepsis can be associated to infective endocarditis (IE) as well.

Endocarditis is defined as "an inflammation of the endocardium" that can be caused and related to different ethiologies/diseases, though large part is caused by infectious agents.

The incidence of IE is between 2 and 10 episodes per 100,000 person-years in most population-based studies[11,12]. IE is more commonly associated with invasive medical procedures, injection drug use and old age[13-14]. About 75% of patients who develop IE have underlying structural heart disease[15].

In the past, rheumatic heart disease with mitral stenosis was the most common valvular defect in patients with IE. Recently, the most common predisposing lesions are mitral regurgitation, aortic valve disease, and congenital heart disease[16.17].

Mitral valve prolapse associated with mitral regurgitation is another risk factor for IE[18]. The presence of a prosthetic cardiac valve is a remarkable risk factor for IE[19] (Table 5).

European data report a IE prevalence ranging from 0,8 to 3% among ICU (Intensive Care Units) patients[20,21].

IE diagnosis is made according to modified Duke criteria; original well-known Duke criteria to make IE diagnosis were formerly proposed in 1994[22]; in 2000 those criteria were revised and slightly modified introducing new updated concepts[23].

It is possible to make diagnosis of "possibile" or "definite" IE according to major or minor and numbers of Duke criteria met, as reported in (Table 3).
Modified Duke criteria are reported on (Table 4).

Estimated rate of ICU admission for complicated endocarditis is 0,8% (congestive heart failure; septic shock; neurological deterioration, in-patient cardiopulmonary resuscitation)[24].

TAB.3 DUKE CRITERIA FOR "DEFINITE" OR "POSSIBLE" ENDOCARDITIS

Definite endocarditis	**Diagnosis**
	2 major criteria and 0 minor criterion
	1 major criterion and 3 minor criteria
	0 major criterion and 5 minor criteria
Possible endocarditis	**Diagnosis**
	1 major criterion and 1 minor criterion
	3 minor criteria

TAB.5 PREDISPOSING FACTORS FOR IE

Predisposing factors for endocarditis	• structural heart disease: reumathic, degenerative, congenital valve disease • prosthetic cardiac valve • invasive medical procedures • injection drug use • older age

TAB.4 MODIFIED DUKE CRITERIA

Major criteria	**Blood culture positive for IE**
	• Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus or Community-acquired enterococci, in the absence of a primary focus or • Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: at least 2 positive cultures of blood samples drawn > 12 h apart; or • All of 3 or a majority of > 4 separate cultures of blood (with first and last sample drawn at least 1 h apart) or • Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer > 1 : 800
	Evidence of endocardial involvement
	Echocardiogram positive for IE defined as follows : • oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • abscess; or • new partial dehiscence of prosthetic valve • new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria	• Predisposing heart condition or injection drug use • Fever, temperature >38°C • Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

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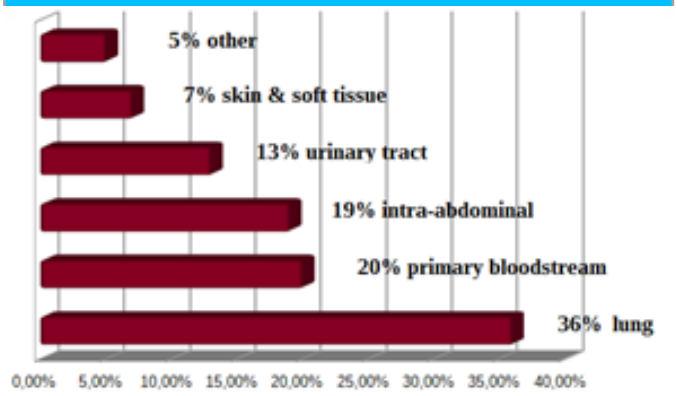
DISCUSSION
IDENTIFYING THE PATIENT

Many predisposing and ethiologic factors as many infectious to be identified foci can lead to sepsis and/or septic shock. Sepsis can or cannot be related to infectious endocarditis and, if confirmed, could possibly be complicated with septic shock as well.
Early ethiologic diagnosis in sepsis is essential for the prognostic judjment, and for reducing complications and implement proper therapeutic strategies[25].

Identifying the patient carrying clinical and instrumental features compatible with suspicion of endocarditis appears then crucial.

We could briefly summarize the epidemiology of infectious foci as follows: 36% lung infections, 20% primary bloodstream, 19% abdominal infections, 13% urinary tract infections, 7% skin and soft tissues infections, 5% all other possible infectious foci[26] (Fig. 1). Thus, only a small proportion of septic patients are actually carriers of active endocardial vegetations. Ruling out the diagnosis is then part of proper diagnostic process.

FIG. 1. INFECTIOUS FOCI LOCALIZATION[26]



Moreover, we need to consider prognostic factors related to IE that we briefly report in table 6. Moreover, we need to consider prognostic factors related to IE that we briefly report in (Table 6).

TAB.6 PREDICTORS OF SEPTIC SHOCK AND IN-HOSPITAL MORTALITY IN IE[27]

Independent predictors of septic shock in IE	Diabetes mellitus
	S. aureus infection
	Concomitant acute renal insufficiency
	Vegetation size ≥15 mm
	Abscesses
	Signs of persistent infection
Independent predictors of in-hospital mortality in IE	Septic shock at anytime
	Heart failure
	Periannular complications
	Signs of persistent infection

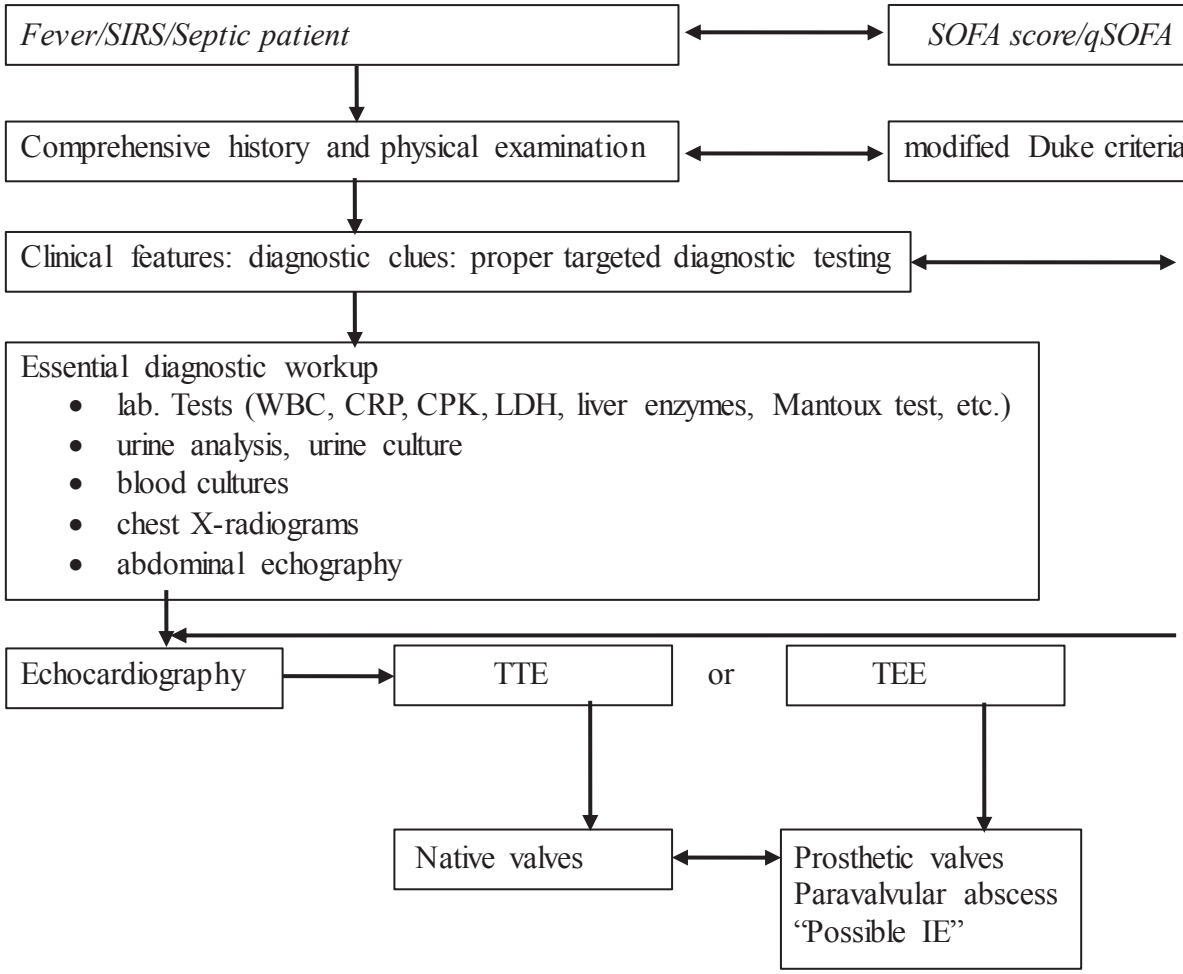
All summarized data have to inform the diagnostic process and direct physician attention towards identification of patient suitable for sepsis related to IE.

DISCUSSION
ECHOCARDIOGRAPHY IN SEPTIC PATIENT

The role of echocardiography in septic patient is well established. Although, role of echocardiography in guiding therapy through haemodinamic evaluation in septic shock patients is well known[28], more accurate use of echocardiography in IE diagnosis is likely needed as this exam is often requested by physicians as a "screening" tool rather than an actual proper diagnostic procedure. Sometimes echocardiography is redundantly performed to assess evidence of heart valve vegetations in SIRS patients or patients with fever of unknown origin (FUO).[29,30]
The echo findings can rule out or confirm diagnosis according to modified Duke criteria. We stress the concept to assess and identify the clinical features according to proper diagnostic criteria: echocardiographic imaging alone is not enough to rule out or confirm diagnosis in septic or FUO

patients and is not a "screening" exam.
We could then introduce a diagnostic flow-chart (Table 7) supporting the diagnosis and improve accurate use of echocardiography merging together the above mentioned information.

TAB.7 FLOW CHART TO SUPPORT ACCURATE USE OF ECHOCARDIOGRAPHY IN FEVER/SEPSIS/SIRS



a: qSOFA (quick SOFA) score defined as:
• Respiratory rate ≥ 22/min
• Altered mentation
• Systolic blood pressure ≤100 mmHg

DISCUSSION
HOW TO/WHAT TO SEARCH FOR

Echocardiography is a wonderful and useful diagnostic exam but requires accurate skill and proper knowledge of the diagnostic technique. We stress the necessity to acquire complete mastery in practical echocardiographic approach undergoing supervised training in high quality and possibly nationally or internationally accredited echo labs following recommendation papers and consensus documents on echocardiography released by EACVI/ESC in order to reduce inter-inter observer variability and stick to the best practice position statements in the field.
(https://www.escardio.org/Guidelines/Consensus-and-PositionPapers/CardiovascularImaging/Echo).
Transthoracic echocardiography (TTE) or trans-esophageal echocardiography (TEE) must be performed as soon as a concrete suspicion of endocarditis occurs, according to clinical complete evaluation and Duke criteria, in order to achieve best earlier and proper therapeutic approach. Essential diagnostic workup has to be clinically and reasonably oriented at the same time, according to clinical

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findings and good, accurate practice. In patients with "possible IE" or suspected complicated IE (i.e., paravalvular abscess) and in patients with suspected prosthetic valve IE, TEE can be performed as initial diagnostic test.
Echocardiographic findings are reported in the table 8 as reported in consensus paper by Habib et al. EACVI/ESC [31,32].

TAB.8 ECHOCARDIOGRAPHIC FINDINGS IN IE [31,32]

Echocardiographic findings [31,32]	
Vegetation	Oscillating or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material
Abscess	Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance
Pseudoaneurysm	Pulsatile perivalvular echo-free space, with colour Doppler flow detected
Perforation	Interruption of endocardial tissue continuity traversed by colour-Doppler flow
Fistula	Colour-Doppler communication between two neighbouring cavities through a perforation
Valve aneurysm	Saccular bulging of valvular tissue
Dehiscence of a prosthetic valve	Paravalvular regurgitation identified by TTE/ TEE, with or without rocking motion of the prosthesis

Moreover **TEE is recommended** in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (i.e.: paravalvular abscess).
Right sided infective endocarditis (RSIE) representing 5-10% of all IE; they are less common than left sided IE and are increasingly associated with e.v. injection (in drug users), cardiac implantable electronic device infection, indwelling lines (hemodialysis, parenteral nutrition and chemotherapy) .
TEE can be useful in differential diagnosis in RSIE as well in all cases mentioned above to improve sensibility and accuracy of diagnosis.

CONCLUSIONS

Echocardiography is a useful exam in confirming or ruling out diagnosis of IE in septic patient.
Echocardiography is not a "screening" exam but an accurate diagnostic tool that has to be included in a proper diagnostic approach according to international guidelines according to modified Duke criteria.
A flow chart is proposed to help diagnostic management in SIRS/septic patient.
The choice of TTE/TEE as initial exam has to be made according to possible or suspected diagnosis of endocarditis and considering the predisposing and prognostic factors of the patients.

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