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Review Article

BIOMARKERS FOR SEPSIS: A REVIEW ARTICLE

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ABSTRACT

Sepsis is a universally prevalent condition in patients that carries a major risk of morbidity and mortality. Early identification recognition of sepsis as the cause of deterioration is desirable desired, so effective treatment active management can be initiated commenced rapidly quickly. Traditionally Conventionally, diagnosis was based established on presence existence of two or more positive affirmative SIRS criteria due to infection sepsis. However Nevertheless, recently recently published issued sepsis-3 criteria put more emphasis prominence on organ dysfunction caused triggered by infection in the definition of sepsis Physicians Clinicians still rely depend on a number of traditional and novel innovative biomarkers to discriminate classify infected and non-infected patients between patients with and without infection, as the cause of deterioration. The aim objective of this review is to focus emphasis on the various numerous biomarkers available. To conclude Procalcitonin, presepsin, CD64, su PAR, and sTREM-1 are the best evaluated biomarkers for diagnosis and prognostication of sepsis to date.(1)It is important significant to test utility efficacy, performance ,and validity strength of future biomarkers before implementing employing them in routine clinical medical care.

INTRODUCTION

Sepsis is defined as 'a life-threatening organ dysfunction caused by a dysregulated host response to infection'.(1) This definition highlights the three critical components of sepsis, namely the presence of infection, the abnormal regulation of the host response to infection and the resulting organ system dysfunction as a result of the host response.The taskforce identified 'life-threatening organ dysfunction' by 'an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more(1).The aim of this narrative review is to give an introduction to the most wellassessed markers that can help informed decision making in patients with sepsis

METHODS

In this article we reviewed various observational articles, clinical and experimental studies from electronic data bases (PUBMED and Cochrane central register of controlled trials) for potentially relevant articles comprising various studies from January 2010 to December 2018 published in English. Key words used are Sepsis, Biomarkers, and SOFA score.

Septic shock

Septic shock has been defined in a variety of ways depending on the clinical variables chosen to characterize its associated organ dysfunction and hypotension. The 2012 taskforce definition of septic shock is 'sepsis-induced hypotension' that persists despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as hypotension (systolic blood pressure (SBP) 40mm Hg or less than 2 SD below normal for age in the absence of other causes), elevated lactate (>1mmol/L) or oliguria (urine output <0.5mL/kg/hour for 2hours despite fluid resuscitation) secondary to infection.(2)

In developing the 2016 guidelines, the taskforce emphasized cellular and metabolic dysfunction as critical factors that differentiate septic shock from sepsis. They came to the following definition of septic shock: 'sepsis with persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate >2 mmol/L (18 mg/ dL) despite adequate volume resuscitation' (2)

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SOFA Score

The Sequential Organ Failure Assessment (SOFA) score is a scoring system that assesses the performance of several organ systems in the body (neurologic, blood, liver, kidney, and blood pressure/hemodynamic and respiratory) and assigns a score based on the data obtained in each category. The higher the SOFA score, the higher the likely mortality. (3)(Table 1)

Table 1 SOFA Score variables and Scoring

Variables	SOFA Score 0	1	2	3	4
Respiratory Pao_2/Fio_2, mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets $\times 10^3/\mu L$‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d‖	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).
‖To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

The quick SOFA score

In addition to using the SOFA score to identify patients with sepsis, the task force also proposed a novel scoring system to rapidly screen for patients outside the ICU who are at risk of developing sepsis: the 'quick SOFA' (q SOFA) score. On statistical review, it had predictive validity that was similar to that of the SOFA score for patients outside the ICU (Table 2)

Table 2 Quick SOFA'' (q SOFA) score

"Quick SOFA'' (q SOFA) score
Patients outside the ICU are at risk of sepsis development if two or more of the following are abnormal:
*► Elevated respiratory rate ≥22 breaths per minute
► Altered mental status (Glasgow Coma Scale score e<15)
► Systolic blood pressure of 100mm Hg or less

Biomarkers of Sepsis

Definition

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"(4)

Biomarkers of sepsis in particular can have an important place in this process because

1. They can indicate the presence or absence or severity of sepsis
2. Helps in prognostication, guiding antibiotic therapy.
3. Evaluating the therapy response and recovery from sepsis.
4. Predicting complications of sepsis and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction).

Current Biomarkers in sepsis

The presently existing sepsis biomarkers are mostly two - C-reactive protein (CRP) and procalcitonin (PCT). These tests are extensively - but not universally - used in the medical practice for adequate sepsis identification and monitoring.(5) Other than thesereal biomarkers, numerous other laboratory tests can be useful for sepsis treatment, including total blood cell count to estimate the existence of leukocytes is or leukopenia, and importantly - serum lactate levels as an index of tissue hypoperfusion. (6)

C-reactive protein

It is an acute-phase protein and labelled as a marker of inflammatory process unrestricted of the cause. It is produced and released by hepatocytes in reaction to cytokines, chiefly interleukin (IL)-6.Subsequent its release triggered by certain cytokines, it itselfacts as a direct inflammatory mediator. The major limiting factor of CRP is the absence of specificity, as it is continuously amplified in SIRS, irrespective of the cause, along with others such autoimmune diseases and cancer, hence it cannot be used as a prognostic marker(7). Due to its small half-life, it may be helpful to monitor the course of certain disorders, including infections(8). Some data suggest that CRP may be used for diagnostic purpose in combination with other biomarkers such as PCT. (9).

Procalcitonin

PCT is a predecessor of the calcitonin and is chiefly secreted by parafollicular C cells of the thyroid. Nevertheless, the increase in PCT appreciated during sepsis is assumed to be secreted from neuroendocrine cells in the lungs and intestine. Normally PCT is cleaved into calcitonin by a particular protease, therefore low or absent levels are measureable in serum.(10)PCT is secreted by several tissues and inflammatory cells in reaction to bacterial toxins, and its cleavage is concurrently repressed; therefore, serum PCT levels may dramatically increase in patients with bacterial infections, thus representing a helpful biomarker for early diagnosis of sepsis in very sick patients.(11)PCT came out to be as the most conspicuous biomarker for the analysis of infective diseases. Off late a growing number of studies have examined the usage of PCT as a biomarker of sepsis, concentrating on its effect on diagnostic presentations and managing of patients. The pronounced attention on this is due to its extraordinary specificity for bacterial infections. The added advantage of PCT is as it has advantageous kinetics as biomarker, with a quick rise subsequent to its induction, and prompt peak levels (within hours after symptom onset).

The prognostic usefulness has also been explored in a meta-analysis of 25 studies with 2353 patients admitted to ICU, Emergency Departments, and general wards there was a statistically significant mean difference between survivors (n = 1626) and non-survivors(n = 727) of −6.02 ng/mL(p =0.003).(12) PCT may also be utilized for treatment monitoring and decision to discontinue antibiotic treatment. In fact, there is increasing substantiation that PCT supervision can condense the period of antibiotic treatment. In recent times, the SAPS trial used the identical decisional criteria of PRORATA established that PCT-supervised algorithms can lessen the length of antibiotic usage. Furthermore, the PCT-guided set had a lesser mortality than the standard-of-care set of patients.(13)In conclusion, as recently discussed, PCT is the most important biomarker of sepsis currently available in the clinical setting but it should be handled with care and only with a profound knowledge of its kinetics and causes of false-positive and false-negative results.

The Newer Biomarkers

Currently, PCT and CRP are the lone markers of sepsis regularly used in the medical practice in most of the countries. A major drawback of these biomarkers is their reasonably low positive predictive value and specificity. Further studies have concentrated on innovative tests with improved specificity, and a number of unique molecules have been recognized and projected for clinical usage. Nevertheless, only a limited number of studies have the dynamic profile, specificity and investigative presentations essential for transformation to the clinical setting. We will briefly review the features of newer biomarkers for sepsis.

Cytokine Biomarkers

As cytokines are key players in the inflammatory response, they are candidate biomarkers for sepsis. Amongst these, tumor necrosis factor (TNF)-a, IL-1β, and IL-6 have been verified for probable medical use. These demonstrate an initial escalation after inflammatory stimulus, quick removal and enormously extraordinary sensitivity. Nevertheless, their specificity is low to be suitable as diagnostic tool. Levels of particular cytokines were linked with infection severity and progression of organ dysfunction, allowing them possibly valuable prognostic markers. However, their use is presently restricted to research.

Cell Surface Markers and Soluble Receptors

Though still experimental and far from medicaluse, this setconsist of particular of the most likely molecules that satisfy almost complete the feature esessential for a perfect biomarker. The biomarkers suggested and preliminarily tried include CD64, soluble triggering receptor expressed on myeloid cells (sTREM)-1, and soluble urokinase-type plasminogen activator receptor (suPAR).

CD64 is a membrane glycoprotein with augmented expression on neutrophils in individuals with bacterial infections. CD64 has a comparatively good specificity and a strong association was established among CD64 expression, positive blood culture and infection seriousness.The biggest meta-analysis of 26 studies comprising an aggregate of 3944 patients found a mean sensitivity and specificity of 0.76 (95%CI 0.74–0.78) and 0.85 (95% CI 0.83–0.86), respectively, with an areaunder the SROC = 0.92. (14)However, the practical quality of these studies is comparatively low and additional studies are required.

sTREM-1 is a soluble form of TREM-1, a glycopeptide receptor upregulated on the surface of myeloid cells after bacterial infections.A latest systematic review evaluating the presentation of TREM-1 as a investigative indicator of sepsis in a SIRS population established sTREM-1 had a modest investigative presentation in distinguishing SIRS from sepsis,with a combined sensitivity of 79% (95% CI 65–89) and a specificity of80% (95% CI 69–88).(15)Basing on existing data, its sensitivity and specificity is comparable to presently used biomarkers, thus a conversion in the clinical setting seems doubtful within the subsequent few years.(15)

uPAR is a surface signalling receptor expressed on most leukocytes. Its soluble form **(suPAR)** is present in plasma and further biological fluids after the disruption of the membrane receptor triggered inflammatory processes. Its utility as prognostic biomarkers are limited, with less specificity and positive predictive value than presently used biomarkers. Conversely, circulating suPAR levels are ominously related to the severity of the inflammatory response and have higher prognostic value over other frequently used biological markers in sepsis .(16)

Other biomarkers

Proadrenomedullin (proADM) is the mid-regional fragment derivative from the cleavage of ADM, produced by the adrenal medulla. proADM is involved in the pathogenesis of hypotension connected with severe sepsis. proADM displayed an higher influence to predict localized bacterial infection and discriminate sepsis from SIRS in patients with hematologic malignancies.(17)

Micro-RNAs (miRNAs) are a freshly discovered class of small, non-coding RNAs that control protein levels post-transcriptionally(18). miRNAs are extraordinarily stable in the circulation and have been projected as diagnostic biomarkers of various disorders such as cancer and cardiovascular disease. Additionally, fresh studies displayed encouraging results assisting the role of single miRNAand/or multiple miRNAs panels (miRNA signatures) for identification and prediction of sepsis.(19)

Presepsin is the soluble form of CD14 that is expressed on the membraneof macrophages and monocytes and involved in the stimulation ofToll-like-receptor 4 in reaction to lipopolysaccharide stimulus and following secretion of TNF-α. Soluble CD14 is released during sepsis.(20)Its physiological role is not completely interpreted, but is connected to phagocytosisand lysosomal cleavage of microorganisms. The initial escalation inserum levels throughout bacteremia, before rises in PCT or IL-6,marks it a significantly useful, primary marker of sepsis. (21)In a single-centre study of 118 ED patients, Kweon *et al*. assessed the performance of presepsin, IL-6, PCT, and high sensitivity CRP to classify between infected and non-infected patients.(22)

Other biomarkers that are under experimental pipeline are: LBP (lipopolysaccharide binding protein), HMGB-1 (high mobility group box 1 protein), MIF (macrophage migration inhibitor factor), and angiopoietin.

Role of High-density Lipoprotein-CHOLESTEROL (HDL-C) in Diagnosis and Prognosis of sepsis*:* They are Nano sized protein-lipid Particles that circulate throughout the body as a major Component of the blood. Lipoproteins have been implicated to play a role in innate immunity. Knowledge of variations in blood lipid levels in patients with sepsis dates to 1980's, when studies showed significantly low HDL-C levels with sepsis, which improved with improvement in sepsis.

In 1993 Levine DM *et al* was the first to explain the protective effect of HDL-C against bacterial endotoxin. They showed, transgenic mice with high HDL-C had high levels of endotoxin bound to HDL-C, low levels of cytokine response and improved survival compared with mice having low HDL-C level.(23). Dimple An and *et al* have measured the Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDLC) and PCT in 121 community acquired sepsis patients and 31 trauma patients at admission to ICU. They have shown that an among the

markers they estimated, PCT and HDL-C are the most effective in discriminating sepsis from trauma., the significance of correlations of PCT with cholesterol fractions is significant with HDL in trauma patients and LDL in sepsis patients. Hence, in the rural setting where PCT valuation is not easily accessible, cholesterol fractions may be used.(24)

Postulated Causes of low HDL in Severe Sepsis are

1. Nullifying of toxic bacterial substances
2. Suppression of lipoprotein production and LCAT activity
3. Rapid clearance of LPS bound HDL-C
4. Decreased activity of ABC 1 activity
5. Augmented Human secretory phospholipase A2 (sPLA2) activity
6. Dilutional effect due to resuscitation fluids. (25)
7. lecithin cholesterol acyl-transferase (LCAT) , ATP-binding cassette transporter ABC1,Secreted phospholipases A2 , (sPLA2), Lipopolysachharide (LPS)

In a study conducted byNareshMonigariconcluded that there is significant relationship of low HDL value on day 1 with mortality. HDL value of 9 mg/dl at admittance had sensitivity of 89% and specificity of 73% calculating the overall death in patients with severe sepsis. Possibility of expiry with day 1 HDL value less than 10mg/dl is 7.01 times the possibility of expiry with day 1 HDL value greater than10mg/dl. Trend of HDL interrelated with result of patients. Rising trend shows improvement in clinical condition and declining trend inferred deteriorating clinical condition.(25)In a study done by Jeyasuriya *et al* lipid profile was done on the day of admission and day-3 of admission and the total cholesterol levels done on day 1 and 3 were compared with disease outcome.(26) Both these studies implied in that increasing trend in HDL level during the period of hospital stay can also be used as an early prognostic indicator of disease outcome and the patients showing increasing trend of HDL levels has increased chances of survival.

Multiple Biomarkers Combination Superior to Single Biomarker

Latest studies showed that a combined biomarkers usage was superior to a single biomarkers that help in prognostication. Numerous models and scoring systems have been suggested, but the assortment of variables that should be comprised in such scores remains a critical challenge. The infection probability score - which uses six diverse variables regularly obtainable in septic patients such as temperature, respiratory rate, heart rate, white blood cell count, C-reactive protein, and Sequential Organ Failure Assessment score - is the most certified, simple and universally available even though its use should be restricted to life-threatening patients.(27)Off late, Bioscore compiling neutrophil CD64, PCT and sTREM-1 showed remarkable diagnostic performances. (28)It remains essential that physicians managing sepsis patients have meticulous understanding of the features, benefits and restrictions of obtainable biomarkers, in addition to their assimilated use inside suitable decisional algorithms, or scoring methods in order to develop the diagnostic performances, therapeutic relevance and patient's results.

CONCLUSION

In the recent years, the enhanced number of high-risk patients along with the selection and dissemination of multidrug-resistant organisms has outstretched fresh tasks in the managing of sepsis. The approach to a sepsis patient begins initially with clinical examination of disease likelihood and severity, so as to classify patients who warrant aggressive resuscitation and timely antibiotic treatment. Beside this, wide range studies have been carried out in order to recognize biomarkers beneficial for diagnosis, classifying severity, treatment and follow-up of sepsis. Up to the present time, though with particular restrictions, the most certified and clinically helpful biomarker is PCT, preferably used in combination with C-reactive protein. Additionally, solid facts support the usage of PCT supervision to safely lessen and enhance the extent of antibiotic therapy. Several other biomarkers are being explored and tried in medical studies.To conclude Procalcitonin, presepsin, CD64, suPAR, and sTREM-1 are the best evaluated biomarkers for diagnosis and prognostication of sepsis to date.(29) However, additional studies are obligatory in advance their use could be rendered into the clinical scenario.

Take Home Message

Various biomarkers are used in diagnosis and prognosis of sepsis. HDL-C measurement in sepsis is very cost effective and freely available. In sepsis the measurement of HDL-Cholesterol has important prognostic implications. A high initial value or rising value of HDL-C is possibly associated with better prognosis and survival. A very low HDL-C or falling values imply poorer outcomes and survival.(25)

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