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Name of the journal- World Journal of Critical Care Medicine

Manuscript no: 84174

Manuscript type: MINIREVIEWS

Biomarkers in sepsis- Looking for the Holy Grail or chasing a mirage!

Ahuja N et al. Sepsis/ Biomarkers in Sepsis

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Abstract-

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) may help to

increase the certainty of diagnosis. Biomarkers have been evaluated in the past for many diseases and have been evaluated for sepsis as well. Biomarkers may find a possible role in diagnosis, prognostication, therapeutic monitoring and anti-microbial stewardship in sepsis. Since the pathophysiology of sepsis is quite complex and is incompletely understood, a single biomarker that may be robust enough to provide all information has not been found as yet. However, many biomarkers have been studied and some of them have applications at the bedside and guide clinical decision-making.

We evaluated the Pubmed database to search for sepsis biomarkers for diagnosis, prognosis and possible role in antibiotic escalation and de-escalation. Clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Commonly studied biomarkers such as procalcitonin, Soluble urokinase-type plasminogen activator (Supar), presepsin, soluble triggering receptor expressed on myeloid cells 1, IL6, C Reactive Protein etc have been described for their possible applications as biomarkers in septic patients.

Conclusion-

The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base continuously. For patients presenting with sepsis, early diagnosis and prompt resuscitation and early administration of anti-microbials (preferably within 1 hour) and source control are desired goals. Biomarkers may help us in the diagnosis, prognosis and therapeutic monitoring of septic patients. The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase.

Keywords- Sepsis; sepsis biomarkers; procalcitonin; presepsin; omics

Neelmani Ahuja, Anjali Mishra, Ruchi Gupta, Sumit Ray. Biomarkers in sepsis-Looking for the Holy Grail or chasing a mirage!

Introduction-

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. It is a leading cause of mortality across the world and is a major healthcare concern [1]. Septic shock is a subset of sepsis in which the underlying cellular/ metabolic abnormalities are profound enough to increase mortality. These patients are identified with the help of clinical criteria of hypotension requiring vasopressors to maintain a mean blood pressure of more than 65 mm Hg and a serum lactate level of more than 2 mmol/L despite adequate fluid resuscitation. Initially, sepsis was defined in 1991 as infection or suspected infection leading to the onset of Systemic Inflammatory Response Syndrome (SIRS) where SIRS was defined as the presence of any two out of four criteria- tachycardia (heart rate > 90/ min), tachypnoea (respiratory rate > 20 breaths per min), fever or hypothermia (temperature > 38 C or < 36 C), leukocytosis or leukopenia (Total Leukocyte Count > 12000/ mm 3 or < 4000/ mm3 or immature forms or bands > 10 %. Rudd et al [2] have attempted to estimate the global, regional and national incidence of sepsis and associated mortality using the Global Burden of Diseases, Injuries and Risk Factor Study estimates. They estimated an incidence of 48.9 million cases (95 % uncertainty interval 38.9-62.9) of sepsis recorded worldwide in 2017. Almost 11 million (10.1-12) deaths were recorded as related to sepsis which is approximately 19.7 % (18.2 – 21.4 %) of all global deaths. In comparison from 1990 to 2017, age-standardized sepsis incidence decreased by 37 % (95 % UI- 11.8-54.5) and mortality decreased by 52.8 % (47.7- 57.5). The highest burden of sepsis was estimated to be in sub-Saharan Africa, Oceania, south Asia, east Asia, and Southeast Asia. Markwart et al [3] in their

study have estimated that around 23.6 % of cases (95 % CI 17- 31.8 %, range 16-36.4 %). Among the patients with sepsis associated with organ dysfunction in ICU, 24.4 % (95 % CI 16.7-34.2 %, range 10.3-42.5%) were acquired during ICU stay while 48.7 % (95 % CI 38.3- 59.3 %, range 18.7- 69.4 %) had a hospital origin. In ICU patients, with hospital-acquired sepsis associated with organ dysfunction, a mortality of 52.3 5 (95 % CI 43.4- 61.1 %, range 30.1- 64.6 %). With this huge burden of sepsis worldwide, there is a pressing need for early and accurate diagnosis of sepsis to allow early initiation of therapy.

The pathophysiology of sepsis is complex and is poorly understood. It involves the activation of various pro-inflammatory and anti-inflammatory pathways in response to a pathogen and its effects on the host. These pathways tend to disrupt the metabolomic profile and the identification of these metabolites can be helpful in diagnosis, therapy modification, and prognostication in sepsis patients.

Early recognition of sepsis and prompt management is essential and can help to reduce mortality in such patients. Differentiation of septic patients from other patients with a systemic inflammatory response due to non-infectious causes is difficult. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) may help to increase the certainty of diagnosis. Early initiation of antibiotics is one of the cornerstones of the management of septic patients. However prudent antimicrobial therapy is required to prevent the emergence of drug-resistant organisms and hence an increased certainty in the diagnosis of sepsis will help to rationalize initiation of anti-microbials and also might help to de-escalate or discontinue them in critically ill patients, thereby reducing the chances of resistance. Biomarkers may serve as an aid for diagnosis, prognosis and therapy modification in septic patients. In the plethora of biomarkers, only a

few have been recognized for their diagnostic abilities, but none have marked their presence as the absolute indicator of sepsis diagnosis.

A biological marker or a biomarker is defined as a character that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. They may be used for diagnosis, staging of disease, prognostication, and for prediction and monitoring of clinical response to therapy. An ideal biomarker for sepsis should have the following characteristics:

Early identification of sepsis to initiate timely antibiotics

High specificity to differentiate from noninfective causes of SIRS

Identify bacterial sepsis from other causes of infection

Prognostication of the patient's condition

Guide antibiotic therapy- escalation and de-escalation of antibiotics

A few biomarkers for sepsis have been described in Table 1. Our review aims to assess the role of biomarkers in diagnosis, prognosis and antibiotic stewardship in septic patients.

Biomarkers for diagnosis of sepsis-

In our review for biomarkers for the diagnosis of sepsis, we searched the Pubmed database for sepsis biomarkers for diagnosis and narrowed the search by selecting biomarkers which have been studied in at least 300 patients or had a meta-analysis done with at least 1000 patients. Biomarkers with an area under the curve (AUC) of at least 0.80 were then individually researched and included (Table 2). Few of the biomarkers and their utility in diagnosing sepsis, have been explained in our review.

C Reactive Protein (CRP)-

CRP is an acute phase reactant which rises early in any inflammatory response including sepsis. Though its specificity has been challenged repeatedly, it is still among the most frequently included parameter in clinical studies. [4]

Procalcitonin (PCT)-

Procalcitonin demonstrated better diagnostic accuracy and specificity compared to CRP [5,6]. Alongside CRP, it is the most extensively studied marker and the most common marker against which most other markers have been compared for their diagnostic and prognostic role in sepsis. It is now well established that its levels rise in sepsis. However, the increase in PCT levels is significantly influenced by the type of infection, the site of infection, the severity of the patient's illness and post-operative status and the type of surgery. It increases within 4 hours of injection of endotoxin, so it has the potential to recognize gram-negative sepsis early. Higher procalcitonin levels are seen in gram-negative bloodstream infections compared to gram-positive infections and candidemia [7,8].

Patients with gram-negative bacteremia had higher procalcitonin levels than gram-positive bacteremia or candidemia [9]. However, Goodlet KJ et al [10] found that PCT failed to rule out bacteremia.

In burn patients, PCT has been shown to be effective for early diagnosis of sepsis (AUC: 0.92) [11].

PCT like many other sepsis biomarkers (CRP, IL6) increases in response to surgery in the first 24 hours. Major cardiac and abdominal surgeries have been found to have higher PCT values. Unlike CRP, PCT levels rapidly fall and any subsequent rise has been shown to corroborate with post-operative sepsis. Dong et al found in post-cardiac surgery PCT was able to identify infective systemic inflammatory response syndrome (SIRS) compared to CRP and WBC ($p<0.0001$) [12].

Procalcitonin-based antibiotic initiation failed to show any short-term mortality benefit rather than a delay in antibiotic initiation in sepsis. Procalcitonin-based antibiotic protocol though has shown its role in the de-escalation of antibiotics [13]. Hence it is imperative to use procalcitonin within a clinical context rather than as a sole marker for the diagnosis of sepsis.

Presepsin (sCD14-ST)-

Presepsin is released from monocytes following infection and in a recent meta-analysis, it is as good as procalcitonin for diagnosis of sepsis with an AUC of 0.87 and sensitivity and specificity of 0.84 and 0.73 respectively. The major limitation was the inclusion of only observational studies and no RCTs [14].

Liu B et al evaluated 859 patients in a single centre presenting in emergency and found that compared to SIRS, patients with sepsis had significantly presepsin values ($p<0.0001$). The value increased with the severity of sepsis. Presepsin had significantly higher AUC than PCT in diagnosing sepsis ($p<0.01$). These findings correlate with that of Romuldo et al in using presepsin to differentiate noninfective SIRS from infections.

Following trauma; PCT, CRP, and total blood count [15] increase irrespective of infective status, unlike presepsin which was found to be significantly increased in infected trauma cases only [16].

Halici A et al found presepsin to be effective in differentiating COPD exacerbation with and without pneumonia[17].

Thus, presepsin has the potential to diagnose sepsis early and also to differentiate sepsis from non-infective SIRS, thereby optimising antibiotic initiation. Further randomised control trials are needed.

Soluble urokinase-type plasminogen activator receptor (SuPAR)-

Soluble urokinase-type plasminogen activator receptor (SuPAR) is normally present in blood and various other body fluids and is increased in states of

inflammation. In the recent meta-analysis by Huang et al SuPAR had a moderate diagnostic ability for sepsis similar to procalcitonin, but was inferior to PCT in differentiating from non-infective SIRS [18].

Neutrophilic CD 64 (nCD64)-

Neutrophilic CD 64 is a surface receptor on the antigen-presenting cells which increases in response to infections and exposure to endotoxins.

In adult patients, Yeh CF et al and Cong S et al found neutrophilic CD 64 outperformed procalcitonin, CRP and IL-6 for sepsis diagnosis [19,20].

Liu Q et al in their observational study found neutrophilic CD 64 to be significantly increased in bacterial and viral infections compared to fungal infections (p value< 0.0005), and in DNA virus infections compared to RNA virus infections(p<0.0071). Further studies may be needed to establish its role to distinguish bacteremia.

In critically ill patients, neutrophil CD 64 when combined with other markers like CRP is useful for diagnosing sepsis, especially when combined with CRP. A normal CRP and neutrophil CD 64 (cut off 230MFI) ruled out sepsis with a 99% probability. An increase of 40MFI may indicate ICU-acquired infection in a previously non-infected patient as per their results [22].

Other biomarkers-

Various markers like IL-27, s-TREM-1, and HMGB-1 failed to perform as diagnostic markers in larger trials [23,24,25,26].

Group IIA secretory phospholipase A2 (sPLA2-IIA) in a prospective cohort analysis could differentiate severe sepsis but needs further studies. Bactericidal/permeability-increasing protein (BPI) in the same study did not show a significant benefit [27].

Combination of biomarkers-

Recent researchers are now also focusing on using a combination of markers with promising results [28]. Novel markers when used with traditional/time-tested clinical tools like neutrophil count, CRP, etc. increases the probability of differentiating sepsis from non-infective SIRS and initiate timely management. PCT when combined with CRP and IL-6 significantly increased its diagnostic accuracy for sepsis [29]. Neutrophil CD64 combined with CRP have shown similar results [22,30].

Timely antibiotic initiation remains the most important factor determining patient survival. At present most biomarkers act as an aid to clinical judgement and not its replacement in the diagnosis of sepsis and antibiotics administration (Table 3).

Biomarkers for sepsis prognosis-

Apart from diagnosis, biomarkers may also be used for prognostication in septic patients. We searched the Pubmed database for biomarkers that have been previously described commonly in literature. We searched for the biomarker in question in the context of prognosis in septic patients. Only clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Some of the biomarkers studied in sepsis patients have been evaluated for prognostication in such patients and results have been promising.

Procalcitonin-

In a meta-analysis conducted by Arora et al [31], procalcitonin levels were found to be significantly lower in survivors of sepsis than non-survivors. Another meta-analysis by Patnaik et al [32] that had 1974 patients evaluated for procalcitonin clearance had an overall mortality of 37.54 %. They concluded that procalcitonin non-clearance can be used as a marker for mortality. However optimal cutoff points for the same for septic patients in ICU are

unknown. An overall area under the curve of 0.708 (95 %CI 0.648-0.769) was observed for the same under the random effect model as a result of moderate variation (50.80 %) in the studies included. So procalcitonin clearance could be used as a predictor for mortality and prognostication in septic patients with non-clearance suggesting a higher risk of death. (Table 4A)

Masson et al [33] evaluated presepsin (a soluble CD 14 subtype) and its relation with mortality in patients with septic shock enrolled in the multicenter ALBIOS trial. 997 patients were evaluated and their results showed that baseline presepsin concentrations increased with SOFA score, the number of prevalent organ dysfunction failures, and the incidence of new failures of respiratory, coagulation, liver and kidney systems. A rise in the concentration of presepsin from Day 1 to Day 2 predicted a significantly higher ICU and 90-day mortality. They concluded that presepsin is an early predictor of host response and mortality in septic patients. (Table 4B)

Adrenomedullin (ADM) and Pro adrenomedullin (proADM)

Adrenomedullin (ADM) and Pro adrenomedullin (proADM) are other markers that could be used for prognostication in septic patients and it is one of the biomarkers that has been evaluated for prognostication in CAP patients (apart from IL6). Christ- Crain et al [34] have described its prognostic significance in CAP patients and concluded that proADM could be used as a risk stratification marker in patients with CAP. Li et al [33] in their observational trial found that higher IL6 levels were associated with higher mortality and bacterial pneumonia patients had the highest IL6 levels as compared to pneumonia of other aetiologies. Li et al [35] evaluated the ability of Adm and proADM for prognosis in septic patients in a meta-analysis and their results showed that increased AM or Pro ADM levels are associated with increased mortality (pooled RR= 3.31; 95 % CI- 2.31-4.75). (Table 4C)

Soluble urokinase-type plasminogen activator receptor (SuPAR)-
suPAR has been evaluated in multiple trials and systematic reviews [18] to assess for prognostication in septic patients and has been validated to be a useful prognostic marker in adult septic patients. (Table 4D)
sTREM 1 could also be useful in predicting mortality in septic patients at an initial stage of infection and has also been used for prognostication in neonatal septic patients [37]. (Table 4E)
Various biomarkers as described above and in the table have been evaluated for prognostication in septic patients. Sepsis biomarkers by itself can provide valuable information for prognostication and in conjunction with organ dysfunction scores and severity scoring systems for critically ill patients can provide an improved assessment for mortality and prognosticating such patients. However, costs associated with their use, limited availability and limited knowledge about them are a hindrance in the clinical application of these markers. The optimal cut-off for prediction for prognosis has not been well defined and there is considerable heterogeneity in the literature. Site-specific values of these biomarkers (such as urine, CSF etc) have not been adequately studied. Procalcitonin is a biomarker that has been used relatively more frequently in many countries and its non-clearance is associated with a higher mortality. The domain of biomarkers for sepsis prognosis is a promising field and many new biomarkers are expected to be discovered with the use of omics technologies.

Role of Biomarkers in Antibiotic Stewardship/De-escalation-
Longer and injudicious use of broad-spectrum antibiotics has been associated with a higher frequency of adverse effects and interference with the

microbiome, more treatment costs and the emergence of antibiotic resistance. Ruling out sepsis with certainty and withholding antibiotics, especially in critically ill patients is a challenging task even for a highly experienced physician. Although a shorter treatment course instead of longer has been recommended by the current Surviving Sepsis guidelines, a definitive duration of treatment for different sites and severity of infection has not been clearly defined [38]. CRP and PCT have been studied extensively in the biomarker-based algorithmic approach including antibiotic initiation and discontinuation.

Procalcitonin-

Based on the multiple RCTs that evaluated PCT to guide antimicrobial treatment in patients with lower respiratory tract infections (LRTI), the current guidelines by IDSA recommend a shorter treatment course for pneumonia under PCT guidance [39]. The ProHOSP trial conducted at tertiary care hospitals in Switzerland included 1359 patients with severe LRTIs and studied the role of PCT in the initiation and discontinuation of antibiotics. The trial concluded a lower mean duration of antibiotic exposure and less frequent antibiotic-associated adverse effects in the PCT group as compared to the control group (standard of care[SOC]) within 30 days from the time of presentation [40].

The PRORATA trial, which was a large trial conducted on 630 critically ill patients with a suspected bacterial infection in France aimed at studying the effectiveness of a procalcitonin-based algorithm to decrease antibiotic exposure. The algorithm included initiation of antibiotic if serum PCT was ≥ 0.5 ng/mL and continuation till the serial measurements showed levels less than 0.5 ng/mL or reduction by at least 80% of the baseline value. The trial results showed a statistically significant decrease in the duration of antibiotic treatment from 11.6 days in the PCT group to 14.3 days in the control arm ($p <$

0.0001). The rate of relapse and re-infection were comparable between the two arms but a trend towards higher mortality in the PCT group at 60 days [41]. On similar grounds, the SAPS trial was designed to study the discontinuation of antibiotic protocol based on serial PCT measurements. The results were similar to the PRORATA trial with a significant reduction in antibiotic exposure days in the PCT group [5 days vs 7 days in the standard of care ($p < 0.0001$)]. However, in contrast to the PRORATA trial, the SAPS trial also found a reduction in 28-day (19.6% vs. 25%, p: 0.0122) and 1-year mortality (34.8% vs. 40.9%, p: 0.0158) [42].

C reactive protein (CRP)-

A systematic review and meta-analysis published by Petel et al evaluated the efficacy of CRP in septic patients. Based on the results of this analysis, the CRP cut-off recommended for antibiotic discontinuation was <10 mg/L for neonatal sepsis. The majority of the studies on adults included patients with respiratory tract infection and cut-offs used were similar, with most of them withholding antibiotics if CRP was <20 mg/L and initiating or continuing the use of CRP was >100 mg/L. The physician's discretion was followed for CRP values between 20 mg/L and 100 mg/L. The meta-analysis concluded that CRP based algorithmic approach reduced the rate of antibiotic initiation with no significant differences in mortality, infection relapse and hospitalization rates [43].

A recent trial conducted in the critical care unit of a university hospital in Brazil by Borges et al compared the days of antibiotic therapy between a CRP-guided protocol and an evidence-based judicious use strategy (not using the marker). The decision of antibiotic discontinuation in the intervention arm was based on serial CRP measurements (if CRP <35 mg/dl or decrease to decrease ≥ 50%). The trial illustrated the efficacy of the CRP-based strategy in reducing the median duration of antibiotic use by 1 day for the index infection episode (6 (5–

8) days in the CRP arm vs 7 (7–10) days in the control arm; p = 0.011). However, despite such promising results, no significant differences were found in terms of antibiotic-free days and survival outcomes between the two arms [44].

Another multicenter RCT, including patients with gram-negative bacteremia with randomization in a 1:1:1 ratio, compared an individualized CRP-guided antibiotic treatment (Duration based on the decrease in CRP levels ◔75% from its peak along with the absence of fever for 48 hours) with a fixed 7-day and 14-day therapy. The primary outcomes of this trial in terms of incidence of clinical failure occurred in 2.4% of patients in the CRP arm, 6.6% in the 7-day arm, and 5.5% in the 14-day arm (difference in CRP vs 14-day arm was –3.1% ; P < .001). The median duration of antibiotic therapy in the CRP-guided group was 7 days. The findings of this study hence concluded that antibiotic duration should not be predefined in the initial phase of illness and use of a biomarker-guided approach may prevent prolonged antibiotic exposure without increasing the failure rates [45].

Considering the results of these trials and meta-analysis, it may be inferred that CRP-guided protocolized therapy allows a lower antibiotic exposure and comparable rates of infection relapse and mortality with the control group

Newer Biomarkers with a Role in antibiotic stewardship-

Presepsin-

Presepsin is a soluble form of CD14 that takes part in pathogen recognition by innate immunity. Masson and colleagues analyzed a subset of data from the ALBIOS trial and studied the relation between the circulating presepsin levels, the host response and mortality in patients with severe sepsis. The study concluded a direct correlation between a rise in presepsin concentration and a rise in SOFA score and the number of organ failures. Baseline levels of presepsin were found to be higher in patients who subsequently tested positive

for bacterial infection (particularly with Gram-negative sepsis). The levels declined gradually in patients with negative cultures and appropriate antibiotic therapy [33]. Xiao et al, published a trial recently, comparing presepsin guidance to SOC in sepsis. In the intervention group, antibiotics were discontinued at serum presepsin concentration of <350 pg/mL or a decline of more than 80% from baseline. Despite more antibiotic-free days in the presepsin group, there was no significant difference in mortality between the two arms [46]. These findings suggest a potential role of this biomarker in guiding antibiotic escalation and de-escalation strategies.

IL-1β and IL-18-

The VAPrapid2 trial published in 2020 was the first trial to use biomarkers (IL-1β and IL-18 from the bronchoalveolar lavage fluid) to improve antibiotic stewardship by the early exclusion of infection in patients with suspected VAP (ventilator-associated pneumonia). Although the trial illustrated the efficacy of studied biomarkers (IL-1β and IL-18) in accurately excluding VAP, it could not achieve the endpoint of showing any statistically significant difference in the number of antibiotic-free days. Certain factors such as reluctance to BAL and non-adherence to the discontinuation protocol by treating clinicians could have contributed to the lack of difference in antibiotic duration between the intervention and control groups [47].

Omics (Genomics, transcriptomics, proteomics and metabolomics) in sepsis-

The host inflammatory response leads to the generation of by-products or metabolites and these have been used as the traditional biomarkers in sepsis. However, omics technology, including genomics, transcriptomics, proteomics and metabolomics are referred to as the systematic measurement at the level of DNA, RNA, protein and metabolite levels and the omics technology has resulted in the delineation of newer biomarkers in sepsis and sub-phenotyping

in sepsis patients. We will explain omics in sepsis in a nutshell as a more comprehensive detail of omics in sepsis is beyond the scope of this review. Genomics is the study of the genome to explain physiological or pathological processes. Variable response and susceptibility of individual patients to infection are different because of genetic factors. Genomics can be used to determine genetic polymorphisms and epigenetic markers that may be used as bioindicators in septic patients. Single Nucleotide Polymorphism (SNP) are a common type of genetic polymorphism and SNP genotyping of various genes may provide important information relevant to sepsis.

Tightly regulated gene expression leads to the regulation of pro and anti-inflammatory responses in septic patients and gene expression study forms the basis of transcriptomics. Micro RNAs (mi RNAs) are short RNAs of 18 to 25 nucleotides that regulate gene expression in target mRNA. miRNA profiling of leukocytes and plasma in septic patients may be used to detect molecules that may be used as biomarkers. Similarly, long non-coding (involved in epigenetic control of gene expression) may be useful to detect diagnostic and therapeutic classes of biomarkers.

All sets of proteins expressed by an organism constitute a proteome and proteomics is the study of the expression, localization, function and interaction of the proteome. Proteomics may thus provide the basis for determining newer biomarkers in sepsis. [48]

Metabolomics was defined way back in the 1990s and defines techniques aimed at measuring metabolites present within a cell, tissue or organism. The underlying principle in genetics describes the flow of information from DNA through mRNA transcripts and the subsequent translation of it into proteins. These proteins take part in tightly controlled metabolic pathways. Metabolome is the terminal downstream product of the genome and consists of all the low

molecular weight molecules (metabolites) in a cell, tissue or organism required for growth, maintenance, or normal function in a specific physiological state. These metabolites generate the phenotype in an organism and these can be detected and measured to provide information about the particular process in question [49]. The pathophysiological pathways of sepsis may lead to inflammatory and anti-inflammatory metabolites being produced and identification of these metabolic products can help to detect sepsis early, and may also help to assess treatment response and estimate recovery [50].

Su et al [51] identified metabolic biomarkers that can be useful to differentiate sepsis from SIRS. They assessed 65 patients (35 patients with sepsis, 15 patients with SIRS, and 15 normal individuals). They used liquid chromatography-mass spectrometry to analyze metabolites in serum samples. They reported significantly lower levels of lactitol dehydrate and S-phenyl-D cysteine and increased S-(3-methylbutanoyl)-dihydrolipamide-E and N-nonanoyl glycine in septic patients as compared to SIRS patients. Patients with severe sepsis and septic shock had low glyecreyl-phosphoryl-ethanolamine, Ne, Ne dimethyllysine, phenylacetamide and D-cysteine ($p<0.05$) in serum. S-(3-methylbutanoyl)-dihydrolipamide-E, phosphatidylglycerol (22:2 (13Z,16Z)/0:0), glcerlyphosphocholine and S-succinyl glutathione were significantly lower ($p<0.05$) in serum (collected 48 hrs before death) of patients who died. These metabolites are reflective of the ongoing metabolome during sepsis and may be used to diagnose sepsis and estimate severity and mortality. However, larger studies are needed for validation.

Conclusion-

Sepsis and septic shock are life-threatening conditions requiring prompt resuscitation and antibiotic administration. The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base

continuously. Sepsis is the result complex interplay of various pathways. A single biological marker may not be an answer for diagnosis, prognostication, follow up and guide to antibiotic escalation/de-escalation in sepsis. Regardless, understanding these sepsis biomarkers and their role in the sepsis pathway can help to further rationalize sepsis management alongside clinical judgement. Early targets for sepsis treatment would be to administer anti-microbials within 1 hour of presentation and source control as early as possible. The 2021 surviving sepsis campaign guidelines suggest against using procalcitonin and clinical judgement to start initial antibiotic versus clinical judgement alone as waiting for procalcitonin may delay antibiotic administration. However, it is suggested to use procalcitonin in addition to clinical evaluation as compared to clinical evaluation alone to discontinue antimicrobials in patients with septic shock with adequate source control. The values of the biomarkers (like procalcitonin, Supar, nCD 64, presepsin etc.) may help guide the therapy by differentiating noninfective SIRS from infective SIRS. A combination of biomarkers has been found to increase their diagnostic accuracy.

The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase. Many have become redundant and many more are still in the running to prove their worth. "Omics" (including genomics, transcriptomics, proteomics and metabolomics) will lead to the discovery of newer biomarkers and their applications in diagnosis, prognosis and therapeutic monitoring are going to increase.