Review

Utility of biomarker in sepsis

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How to cite the article: Gupta N, Agarwal A. Utility of biomarkers in sepsis. OncoCritiCare2023;1:37-40.

The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1]

As intensive care units are now protocolising management of sepsis and septic shock in accordance with the surviving sepsis recommendations, the mortality rate of patients with sepsis has reduced significantly, but still continues to be unacceptably high.

With the proportion of culture-negative sepsis being as high as 28% to 49%,[2] where no microbiological proof of an infectious focus is found, diagnosing sepsis many a times poses a challenge to both clinicians and microbiologists.

The increasing rates of inappropriate antibiotic use and the worldwide prevalence of antimicrobial resistance further add to the necessity of diagnosing sepsis at the earliest, enabling prompt and appropriate initiation of treatment.

Biomarkers have a critical role to play in early diagnosis of sepsis. In addition, they can help in a multitude of other ways - by indicating the severity of sepsis, differentiating bacterial from viral and fungal infection, predicting organ dysfunction, helping in prognostication, in antibiotic stewardship and even in evaluating the response to therapy.

Sepsis begins with the activation of an innate immune response mediated by the detection of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) on host cells. Subsequently, pro-inflammatory and anti-inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) are released, followed by a rise in the levels of acute phase proteins such as procalcitonin, pro-adrenomedulin, pentraxin-3, and C-reactive protein (CRP). In addition, the serum levels of glycoproteins on cell membranes such as presepsin, soluble triggering receptor expressed on myeloid cell 1 (sTREM-1), and soluble urokinase plasminogen activator receptor (suPAR) may be upregulated, and the expression of CD64, an immunoglobulin receptor, may also be increased.

Owing to this complex pathophysiology of sepsis involving multiple mediators of inflammation, more than 100 different molecules have been proposed as useful biomarkers of sepsis, much more than for any other disease.

While no single biomarker has proven to be a specific indicator of sepsis, rapid detection of key biomarkers could provide the clinician with useful information thereby helping in guiding the treatment.

This review will focus on the diagnostic and prognostic potential of some of the traditional as well as few of the new promising biomarkers.

C–reactive protein (CRP)

CRP, a widely used biomarker to diagnose sepsis, is a protein synthesized by the liver and upregulated by IL–6. It is an acute phase reactant produced in response to nonspecific inflammation, infection and even tissue damage. It helps in the recognition and clearance of foreign pathogens by binding to phospholipids and activating the classic complement pathway. CRP is usually able to differentiate between viral and bacterial infections with levels more than 50mg/dl being associated with bacterial infections 90% of the time.[4] Numerous studies have reported the high sensitivity of CRP for the diagnosis of sepsis, although its low specificity is a primary drawback. The role of CRP in prognostication and predicting increased risk of organ failure is still controversial.[5]

Procalcitonin (PCT)

PCT is a precursor of calcitonin produced by C-cells of the thyroid gland and was first described for the diagnosis of sepsis in 1993. It has since been used widely as a potential biomarker for sepsis. Elevated levels (up to 5000-fold) are seen in response to bacterial toxins within 2 to 4 hrs. In contrast, viral infections downregulate the procalcitonin levels. The diagnostic accuracy of PCT for sepsis has been found have a median sensitivity and specificity of 79%. Higher PCT levels have been associated with increased mortality rates.[6] Moreover, research has shown that PCT levels less than 0.1 ng/mL have been shown to have a high negative predictive value (96.3%) for excluding bacterial infections.[7] Subsequent large, multicentre studies, including the PRORATA trial and the Stop Antibiotics on Procalcitonin Guidance Study (SAPS) validated the use of PCT-guided therapy and showed that PCT can help to reduce antibiotic exposure by shortening treatment duration.[8] Despite being routinely used in clinical practice, PCT has some limitations and has shown to be risen in several other inflammatory conditions aside from bacterial infections such as trauma and surgery.

Cytokines

Another set of biomarkers used commonly in patients of sepsis are the cytokines. Traditionally, the host immune response to sepsis was thought to be characterized by two sequential stages: The initial hyperinflammatory response, where the innate immune system releases proinflammatory cytokines to combat infection by recruiting members of the adaptive system to mount an intense immune response , and , the subsequent stage of compensatory anti-inflammatory response syndrome (CARS), which is a systemic deactivation of the immune system tasked with restoring homeostasis from an inflammatory state. Recent data however suggest that both aspects of the proinflammatory and anti-inflammatory stages of the host immune response often occur concurrently.

Both Proinflammatory markers like TNF-α, IL-1, IL-6, and IL-8, have been shown to be overproduced in sepsis with increased levels showing worsened mortality.[9] Similarly IL 10, the main contributor to CARS has been shown to be high in patients of severe sepsis.[10] However, these cytokines lack specificity as they are also upregulated with sterile inflammation (SIRS), post-surgery, autoimmune disorders, viral infection, and transplant rejection. Additionally, the high cost involved and the difficulty in interpreting these many different cytokines while looking for patterns of upregulation and/or suppression in its relation to the diagnosis of sepsis has proven to be difficult.

Angiopoietins

Angiopoietins (Ang-1 and Ang-2) have been found to be associated with vascular leakage, inflammation, and breakdown of the microvascular endothelium, and therefore have been studied as potential biomarkers in sepsis. While studied mainly in proliferative diseases such as cancer, they have also been associated with inflammation. Ricciuto et al demonstrated that low Ang-1 levels at admission were associated with poor outcome and remained a significant predictor of mortality throughout a 28-day period, while Ang-2 levels correlated with disease severity along with organ dysfunction with levels correlating with tumour necrosis factor-α (TNF-α) and IL-6 levels.[11]

Neutrophil CD64

Neutrophil CD64, a leukocyte surface antigen, also known as Fc receptor 1 (FcR1), is a high-affinity receptor present on neutrophils which binds to monomeric IgG and is involved in both innate and adaptive immune responses by stimulating either phagocytosis or antibody -mediated cytotoxicity. Its expression gets strongly upregulated in response to proinflammatory cytokines of infection within 4–6 hours .[12] Several studies which have looked at neutrophil CD64 expression as a potential biomarker/indicator for detection of sepsis/infection in adults, children, and neonates have demonstrated its higher sensitivity and specificity than CRP, WBC count, neutrophilic and eosinophilic granulocyte counts and even Procalcitonin and IL–6, implying that CD64 index can differentiate between sepsis and SIRS patients in various patient populations.[13]

Soluble Triggering receptor expressed on myeloid cells-1 (sTREM-1)

TREM-1 is a recently discovered member of the immunoglobulin superfamily that is expressed on myeloid cells -1, surface of neutrophils and macrophages. Its expression is upregulated on cells in the presence of bacteria and fungi, but not so in response to non -infectious inflammatory triggers. Its soluble form Strem-1 can be assayed by ELISA from body fluids like plasma, plueral fluid, bronchoalveolar lavage, urine etc. In a clinical study, plasma sTREM-1 levels higher than 60 ng/mL were found to be more accurate than any other clinical or laboratory finding for

indicating infection. A meta-analysis of 11 studies (1795 patients) showed that the pooled sensitivity of plasma sTREM-1 for the diagnosis of sepsis was 79% and the specificity was 80% , thereby concluding a moderate diagnostic performance in differentiating sepsis from SIRS.[14] In another study sTREM-1 was shown to be a mortality predictor as well from infection in a tropical, middle-income country.[15] While studies evaluating sTREM-1 as a potential biomarker are promising, many of other studies contradict whether sTREM-1 has any clinical value, thereby necessitating further analysis.

suPAR

The soluble form of urokinase type plasminogen activator receptor (suPAR) is expressed on various immune cells and is involved in a variety of immunological functions including cell migration, angiogenesis and fibrinolysis. Higher serum levels of suPAR are associated with a higher mortality in patients with an inflammatory response. A recent meta-analysis analysing 17 studies (2,722 patients) reported a AUC of suPAR for discriminating between sepsis and SIRS as 0.81.[16] Many other studies have reported prognostic role of suPAR as well. Other study showed that the mortality rate of bacterial infection increased by 3.37 times with the elevated suPAR level.[17] Owing to its short turnaround times and low production cost, suPAR appears to be a promising biomarker.

Presepsin (sCD14)

Presepsin is a subtype of Soluble N-terminal fragment of the cluster of differentiation marker protein CD14 is expressed on macrophages /monocytes and serves as a receptor for lipopolysaccharides (LPS). In the immune response to sepsis, the serum levels of presepsin are elevated before procalcitonin or IL-6, so it has been proposed as a potential biomarker for the diagnosis of sepsis .[18] A recent prospective study has reported that the serum levels of presepsin in patients with severe sepsis correlated with the SOFA score and presepsin was better than procalcitonin as a biomarker to assess sepsis prognosis and therapeutic effect.[19] Nevertheless, further in-depth analysis of its prognostic value is required

Adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid peptide that is produced mainly in endothelial cells and vascular smooth muscle cells. It is an important mediator of vasodilation and is involved in the regulation of systemic circulation as an autocrine/paracrine vasoactivator. ADM levels are noted to be 20–30 folds higher in septic shock. The mid-regional fragment of pro-adrenomedullin (proADM), is more stable than the ADM peptide, and its levels can be measured in biological fluids. ProADM has been identified in several studies as a prognostic marker for the prediction of mortality in sepsis and septic shock patient. A prospective study at a single centre in Korea measured bio-ADM levels in 215 patients diagnosed with sepsis and septic shock. The levels of bio-ADM in the septic shock group were significantly higher than in the sepsis group, and there was a significant difference between the levels of bio-ADM in the non-survivor and survival groups. The AdrenOSS-1 study also found the levels of bio-ADM to be higher in septic shock patients than in sepsis patients .[20] Since the recent development of the double monoclonal sandwich immunoassay enables bio-ADM measurements, further evaluation, will be required for the clinical use of bio-ADM as a sepsis biomarker.

Intestinal Microflora

The intestinal microflora plays an important role in the development and maturation of the immune system. The intestinal microbial metabolite profiles of sepsis patients were completely altered compared to healthy people and was found to be associated with an increase in mortality. In a recent study, it was found that the microbiota in sepsis patients is rich in microorganisms related to inflammation, such as *Parabacteroides*, *Fusobacterium*, and *Bilophylloma*. Non survivors showed an abundance in Enterococcus species in their instentinal microflora.[21] However, presence of many confounding factors which cause disruption of the intestinal microbiota such as antibiotic therapy and hospitalization, warrant further studies to understand sepsis associated dysbiosis and its use as potential biomarkers. Research on newly identified classes of biomarkers such as microRNAs, long-non-coding RNAs, or the human microbiome are underway and further clinical studies are warranted to understand their roles as potential biomarkers.

Conflict of interest: Nil

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Review

Dual modes of ventilation

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How to cite the article: Pradhan D. Dual modes of ventilation. OncoCritiCare2023;1:41-44.

Conventional modes of ventilations are popular because they are simple, well understood, easy to troubleshoot and most widely used. Often these common modes are not able to match patient specific requirements. Comfort comes at the cost of complexity, over the years, the incorporation of advanced algorithms and closed loop control have allowed delivery of volume assured breaths with variable pressure control. They are also known as dual control modes and can be classified into three groups .[1]

Intra-breath	Inter-breath		Combination
	Pressure limited: Flow cycled	Pressure limited: Time cycled	
VAPS Paug	VSV Variable PS	PRVC AutoFlow VC+ Adaptive pressure ventilation Variable PC	ASV Automode

Table 1: Various types of Dual mode ventilation

Presence of the term "volume" in the name often creates a false impression that these modes are volume controlled, but they are pressure-controlled modes with targeted volume delivery. Also, the use of various proprietary names by different manufacturers creates an impression that each name is a unique mode although all are similar in function. In dual modes, ventilator adjusts the peak inspiratory pressure based on the patient's airway resistance and compliance to deliver a minimum tidal volume (VT) with desired pressure limits. [1,2]

Dual modes have two options: control option for patients with inadequate respiratory drive and support option for spontaneously breathing patients. In control option, VT and respiratory rates (RR) are pre-set for time triggered breaths and patient triggered breaths are supported targeting the minimum VT within appropriate pressure limits. In the control option, the dual control is provided between breaths, changes needed to meet VT and pressure goals are made between breaths based on the previous breath. The support option allows the patient to breathe spontaneously but provides support to achieve the set VT within each breath. This means that if the patient is not on target to meet the minimum tidal volume goal, the machine will augment respiration to achieve the goal within the breath. Patient's contribution towards the set tidal volume target determines the amount of support to be provided by ventilator. The set parameters for dual modes include VT, sensitivity, PEEP, FiO_2 for support modes, and rate and inspiratory time (Ti) added in the control modes. [1,2,3]

Pressure augmentation/ Volume assured pressure support: In pressure augmentation (PAug) or volume-assured pressure support (VAPS) mode, every breath is having dual control-targeted volume delivery and pressure limitation. VAPS is the term used to describe this mode on the Bird 8400st (CareFusion, Viasys Corp, San Diego, Calif.). Breaths are patient triggered (not appropriate with deep sedation, use of muscle relaxants and patients with ineffective inspiratory triggering) and pressure supported to achieve targeted tidal volume. The set parameters include desired VT, minimum RR, inspiratory gas flow, sensitivity settings, pressure above the base line. The algorithm explains the working principle of VAPS/PAug mode.[4]

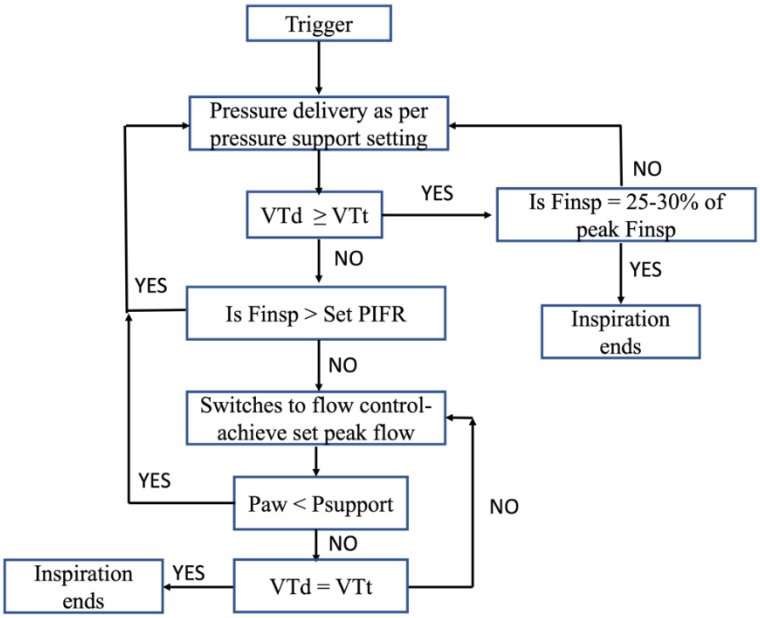

Figure 1: Algorithm for volume assured pressure support mode

Pressure-regulated volume control: Pressure-regulated volume control (PRVC) was first introduced in Servo 300 ventilator during 1990s. It has been in use under the same name in various ventilators such as - Servo-i and Servo-s from Maquet, Inc, Wayne, New Jersey and the CareFusion AVEA from CareFusion, Inc., Yorba Linda, California. PRVC has been used under various different proprietary names - AutoFlow on the Dräger Evita E-4 (Dräger Medical Inc., Telford, Pennsylvania), and VC+ on the Covidien PB 840 (Covidien, Puritan Bennett, Boulder, Colorado), Adaptive Pressure Ventilation (APV) on the Hamilton G5 and C3 ventilators (Hamilton Medical, Bonaduz, Switzerland) (explained below).[4]

PRVC breaths are patient- or time-triggered, volume-targeted, pressure controlled and time cycled. As described in the algorithm (Figure-2), control is from breath to breath. Troubleshooting is required when the pressure alarm goes off indicating the need of higher pressure for the targeted VT delivery. As the compliance improves ventilator keeps reducing pressure control till it reaches the set PEEP. Beware of hypoventilation when the targeted tidal volume (VTt) and the maximum pressure alarm settings are incompatible.[4]

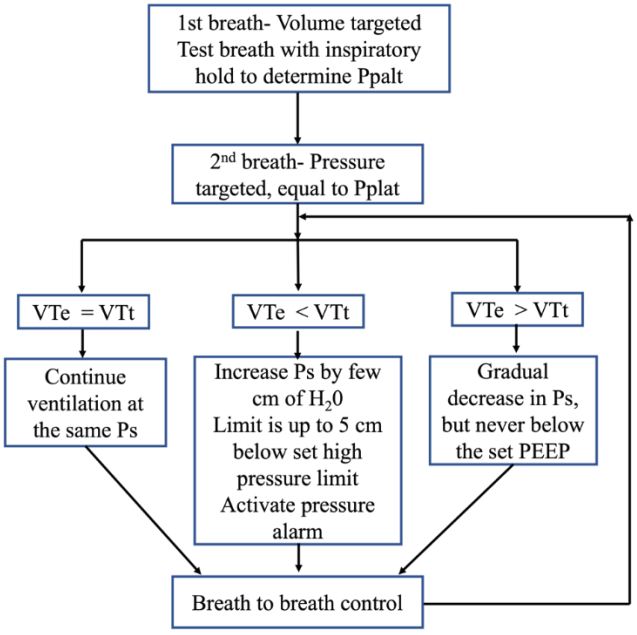

Figure 2: Algorithm for pressure regulated volume control mode

Autoflow mode in a Drager ventilator works on the same principle as that of PRVC. As soon as autoflow is enabled in a VC-SIMV or VC-AC mode, it does not alter the cycling characteristics, rather it regulates inspiratory flow and inspiratory pressure during the mandatory breaths. Also, it improves breathing comfort, especially if spontaneous breathing interacts with mandatory breaths. In such situation, AutoFlow provides gas flow according to the patient's needs and prevents air starvation. The level of pressure support is not affected by AutoFlow and remains same as conventional volume-controlled ventilation. Autoflow mode should not be confused with Automode available in Servo-i ventilator (PRVC + VS). [4]

Adaptive pressure ventilation: These modes are similar to PRVC and available in Hamilton Ventilators (Hamilton Medical, Bonaduz, Switzerland) and can be APVcmv or APVsimv based on breath sequencing. The ventilator automatically regulates the inspiratory pressure and flow to maintain a target tidal volume. The operator sets the target VT, the rate, the PEEP and the high-pressure alarm limit. The ventilator then compares the measured VT to the target VT and adjusts the PIP to the lowest level possible to achieve the target VT. The rationale behind volume targeting is to avoid the variations in VT that may result from changes in lung compliance while undergoing pressure-controlled ventilation, as these may cause ventilator induced lung injury.[5]

Volume support ventilation: Volume support ventilation (VSV) is very similar to PRVC. It is a pressure supported breath triggered by patient with volume target and flow cycling. This is purely a spontaneous mode with a backup mode for the event when patient becomes apnoeic. As with PRVC, the ventilator adjusts the pressure, over several breaths, to achieve the set volume. If volume is too low, then pressure is increased. Conversely, the pressure is reduced if the volume is too high. VSV can be used for patients who are ready to be weaned from the ventilator and can breathe spontaneously. Unlike PRVC which is time cycled, VSV is flow cycled, expiratory valve opens as flow drops to a set percentage of peak flow. It also can be time cycled (when Ti is prolonged for some reason) or pressure cycled (when the pressure rises too high). [4]

Adaptive support ventilation: Adaptive support ventilation (ASV) is a closed-loop mechanical ventilation which combines Pressure support ventilation (PSV) (when the spontaneous RR higher than the target), Pressure control ventilation (PCV) (if no spontaneous breathing effort) and Synchronised intermittent mandatory ventilation (SIMV) (spontaneous RR is lower than the target). It automatically adjusts the support intra-breath as well as inter-breath to optimize the work of breathing (WOB).[6] It uses the Otis *et al.* and Mead *et al.* equation developed in 1950, that states that for a given level of alveolar ventilation, there is a particular RR which achieves a lower WOB. More physiological and individualised ventilation is provided in an energy efficient manner while minimizing the cumulative effects of elastic and resistive load.[7]

The set parameters include height of the patient (in cm, to calculate ideal body weight and dead space 2.2 ml/kg), gender, % minute volume {range 25-350%, normal 100%, asthma 90%, acute respiratory distress syndrome (ARDS) 120%, others 110%, add 20% if temperature >38.5°C (101.3°F) or add 5% for every 500 m (1640 feet) above sea level, trigger: flow trigger (2 l/min), expiratory trigger sensitivity: start with 25% and 40% in Chronic obstructive pulmonary disease (COPD), tube resistance compensation (100%), high pressure alarm limit, PEEP and FiO_2. It starts with few test breaths to obtain measurements and the adjusts the respiratory parameters. Ventilation is pressure and volume limited and % minute ventilation can be titrated according to clinical criteria and blood gas results.[6]

Lack of precise tidal volume control in most of the currently available dual control modes may lead to large variations in VT and associated lung injury, especially in patients requiring low-tidal-volume ventilation.[1,3] Inaccurate feedback (large leak or malfunctioning of sensors) will lead to inappropriate ventilatory output. Modes dependent on physiologic models should be able to measure the model parameters accurately (Inability to measure the compliance and or plateau pressure in patients with high respiratory drive). Mathematical calculations should fit the actual patient, for example incorrect assumptions of ratio of dead space to VT, normal minute ventilation requirement will compromise appropriate delivery of ASV.[8]

Mechanical ventilation has evolved to provide physiological, personalised and high-fidelity respiratory support while allowing the patient to recover from their disease process. In future though ventilators will be able to initiate, maintain, wean and escalate or deescalate ventilatory support without much user interference, but the user need to know the mechanics of these modes and their limitation to be able to take over the control when machines fail to save humanity and also not to forget the science behind mechanical ventilation.

Conflicts of interests: Nil

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