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New Biomarkers of Sepsis with Clinical Relevance

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Abstract

A 2016 task force convened by multiple societies proposed a new definition of sepsis, termed Sepsis 3. The new clinical diagnosis of sepsis is based on variation points in the Sequential (Sepsis-related) Organ Assessment Score (SOFA) and excluded Systemic Inflammatory Response Syndrome (SIRS) as a criterion for defining the diagnosis. Although the new definitions have provided improvements in understanding the disease, the main concern generated by Sepsis 3 is the reduced sensitivity to detect cases that might have an unfavorable course, mainly in early conditions. By limiting the diagnosis to organic dysfunction, the new concept tends to select a more severely ill population. In this way, biomarkers to diagnose sepsis may allow early intervention, which can reduce the risk of death. Although lactate is currently the most commonly used biomarker to identify sepsis, other biomarkers may help to enhance lactate's effectiveness and may be used as a tool for staging the disease, prognosis, and response to intervention. The objective of this chapter is to present possible new biomarkers that are clinically relevant.

Keywords: biomarkers, cytokines, haptoglobin, lactate, sRAGE, sepsis

1. Introduction

The first definition of sepsis was described in a consensus conference in 1991. Known as Sepsis 1, it advocated the hypothesis that infection was directly proportional to the systemic inflammatory response syndrome (SIRS). Ten years later, in a new conference (Sepsis 2), the SIRS diagnostic method was already questioned by the scientific community about its low specificity. However, in the current situation, Sepsis 2 did not offer many alternatives because of the lack of evidence to substantiate the above arguments [1, 2].

Although SIRS criteria have been described for more than three decades as a host's clinical expression to systemic infection and have contributed greatly to the understanding of sepsis in various pathophysiological areas, the need for a new conference in 2016 was recognized, where the sepsis' concepts were reviewed again [2, 3].

Sepsis 3 was proposed by the Society of Critical Care Medicine (SCCM) together with the European Society of Intensive Care Medicine (ESICM), which established that the disease is linked to life-threatening organic dysfunction that is secondary to the body's unregulated responses to the infection. This new definition extinguished the term of severe sepsis and completely abandoned the use of SIRS in the diagnosis of sepsis [4].

In order to promote a new and more sensitive diagnostic method than the previous one, the score of sequential organ failure assessment (SOFA) was instituted. Due to the complexity of the SOFA's rapid completion and the concern of the impossibility of a fast and early disease identification, "quick SOFA" (qSOFA) was also established in Sepsis 3 [3].

Despite the improvements obtained through Sepsis 3, in the same year of the new guidelines, Williams et al. [4] demonstrated in 2016 that the new diagnostic model is not very sensitive in the early stages of disease. These observations are of great clinical relevance because the treatment of sepsis is more effective in early stages.

One of the alternatives used for the early diagnosis of patients in several diseases is the Point-of-Care Testing (POCT), a laboratory test carried out in the places where the intensive treatment is done. POCT has become popular among physicians because its agility in the patients' diagnosis has been shown to be effective, including requiring fewer samples collected from the patient [5].

Unlike traditional laboratory tests, POCT does not require a permanent dedicated space, since it has kits and instruments that can be transported to where the patient is, thus immediately allowing the dosage of several substances, not only in hospital or professional environments, and can be operated by patients in their home [6].

Currently, POCT is used to test a range of pathological conditions, including diabetes, hypertension, hyperlipidemia, and asthma, as well as monitoring of bone density, body composition, and anticoagulation, and these tests are expanding rapidly (from 12 to 15% annually) [6].

Despite the great validity of the POCT test, this method presents operational and environmental instability and is difficult to standardize in intensive care settings [7, 8]. In addition, the clinical status of patients with sepsis is very unstable and the disease severity usually changes abruptly [1]. Thus, it is necessary to recognize new specific and sensitive biological markers for the sepsis diagnosis.

Biomarkers were defined by the National Institute of Health as a characteristic that should be measured and served as an indicator of a normal, pathological state or a response to a pharmacological agent. They shall be characterized by accuracy and reproducibility and may be used as important tools for diagnosis, as well as promoting early diagnosis, indicating the stage of the disease, prognosis, and mechanisms of intervention.

More than 100 biomarkers have already been described and proposed for sepsis; combinations between them have also been demonstrated. However, due to the different stages of severity observed in sepsis in the most diverse populations, it has been complicated to define which marker can be used as a parameter to improve therapeutic strategies. Therefore, for sepsis, a good biomarker has to be able to identify early alterations in order to prevent multiple organ dysfunction and consequently reduce the mortality of patients with this pathology.

New biomarkers could promote better monitoring of the patient's condition and, possibly, a more accurate definition of the disease prognosis. This chapter aims to describe the biological markers already established for sepsis, as well as to cite those that in our opinion show promising results.

2. Established biological markers

2.1 Lactate

Lactate (or lactic acid) is the anaerobic glycolysis end product, and its blood levels increase significantly in the hypoperfusion or hypoxia cases. Due to an

imbalance between lactate production and lactate clearance in patients with sepsis, hyperlactatemia is a common condition in these patients [9, 10].

The first study that connected the production of lactate with sepsis was performed by Bakker et al. [11] in 1991. In this study, they demonstrated that the tissues of patients with sepsis or septic shock did not adequately use the O₂ molecule and that survivors of the disease had lower blood lactate levels than those who died from the disease.

Five years after this finding, Bernardin et al. [12] demonstrated that the changes in the blood lactate level occur within the first 24 hours of treatment, and in addition to blood pressure fluctuation, may be strong indicators of short-term survival prognosis in patients diagnosed with septic shock.

In a paper published in 2013, a Brazilian clinical care research group has demonstrated that hyperlactatemia can be caused by mitochondrial dysfunction and the use of adrenergic drugs in the condition of septic shock [13]. Léguillier et al. [14] demonstrated in 2018 that the lactate dosage, associated with POCT, bring a possible new strategy for the early treatment of patients with suspicion of sepsis [14].

As predicted in Sepsis 3, the most common use of lactate dosage is in the differentiation between sepsis and septic shock in intensive care units (ICUs), and this information is very important and useful for medical professionals.

However, Guo et al. [15] demonstrated in their study that an isolated and simple dosage of arterial lactate is not satisfactory in recognizing the sepsis prognosis. Therefore, they suggest that such dosages need to be supported by results from other biological markers, such as C-reactive protein (CRP), B-type natriuretic peptide (BNP), and N-terminal proBNP (NT-proBNP).

2.2 C-reactive protein

C-reactive protein (CRP) is an acute inflammatory phase protein produced in the liver, currently believed to be a reliable indicator of inflammation and tissue damage, as it is elevated in cases of infection, inflammatory response, damage, and necrosis of the tissue [16]. Among its actions are platelet activation, chemotaxis acceleration, and enhancement of cell-mediated immunity by promoting phagocytosis [17].

One of the first studies to correlate CRP with sepsis was conducted in 1987 by Mustard et al. In this study, it was observed that postoperative CRP levels can predict septic complications even before its clinical manifestation [18].

This protein is also used to differentiate the sepsis of a noninfectious systemic inflammatory response syndrome in trauma patients, in which the high level of this protein in the first 4 days after injury is a reliable indication of infection [19].

In 2013, a study conducted at the Department of Pediatrics at Yonsei University of Medicine showed that high levels of CRP in the mother may indicate a risk of infection of the newborn and that these values would be related to the severity of the disease presented by these babies [16].

Also, in 2013, Oliveira et al. [20] compared CRP with another established biomarker, procalcitonin (PCT). In this study, it was observed that the protein is as effective as PCT to guide antibiotic therapy in patients with sepsis, showing that the group guided by CRP levels required less treatment time when compared to the control groups.

In a study published in 2017, Wang et al. [21] once again correlated CRP with sepsis when comparing the CRP's serum level with those of other proinflammatory cytokines, suggesting that this would be a potential target for the treatment of patients with sepsis.

However, although there is considerable sensitivity in the CRP oscillation to describe the disease intensity in already diagnosed patients, this biomarker has low specificity in determining sepsis, which prevents CRP from being alone an indicator for the diagnosis of the pathology [15].

2.3 B-type natriuretic peptide

B-type natriuretic peptide (BNP) is a cardiac hormone with natriuretic, diuretic, and vasodilatory properties. It is produced by the ventricular myocardium in response to the stretching of the cardiac muscle, having as its main role the cardiac pressure regulation and homeostasis of the intravascular volume [22]. In this sense, septic shock is recognized as a condition that causes severe changes in blood pressure.

BNP or its inactive N-terminal proBNP cleavage product (NT-proBNP) is mainly used as a biomarker for congestive heart failure [23]. However, Papanikolaou et al. [24] demonstrated in 2014 that the severity of sepsis is the major determinant of BNP increase in the disease-induced myocardial depression in patients with a septic shock. In addition, the same study suggests that the increase in BNP serum levels on the second day of the condition is a strong indication of a poor prognosis.

However, due to the inconsistency of results and the specificity limitations, harsh criticism of this biomarker use has recently arisen, demonstrating the need for further studies to validate the use of this as a biomarker in the sepsis condition [25].

It is currently believed that BNP and NT-proBNP have moderate potential to assess the diseased patients' prognosis. As Bai demonstrated in his meta-analysis published in 2018, the peptide can be used as a tool for defining how the condition will evolve, but further studies are needed to assess the real importance of BNP in the clinic [26].

2.4 Procalcitonin

Procalcitonin (PCT) is a prohormone precursor of calcitonin produced by thyroid C cells. Under normal conditions, PCT is not detected in the circulation; however, in situations of great stress, such as sepsis, it is possible to observe a high extrathyroidal production of PCT. PCT is currently used as a tool to differentiate bactericidal infection from other inflammatory and infectious processes [27].

PCT is correlated with sepsis since 1993 when Assicot et al. [28] demonstrated that this protein was detectable in the plasma of diseased patients and with other types of infection. Since then, studies have demonstrated the efficacy of this tool in the prognosis of patients with sepsis, as demonstrated in the review published in 2001 by Meisner [29], in which it was observed that the PCT's concentration during the sepsis and SIRS stages is high and is directly proportional to the severity of the condition.

This method provides additional information to the diagnosis by other parameters of an inflammatory response; such additional information is not provided by conventional parameters of systemic inflammation. Mustafić et al. [30] also demonstrated in 2018 that it is possible to use PCT to reveal the disease severity and prevent a fatal outcome for the patient with sepsis.

In the same year, Bilgili et al. [31] demonstrated that PCT can differentiate even gram-negative bacteremia from a Gram-positive one, noting that protein values are higher in patients infected with Gram-negative bacteria. However, in these cases, PCT should be used only as a support tool for predictive purposes in diagnostic tests.

Biomarker	Sensitivity (%)	Specificity (%)	AUC	NPV	PPV	References
Lactate	58.3	88.1	0.66	78.7	73.7	[33]
CRP	66	80	0.81	88	51	[34]
Pro-BNP	70.8	47.6	0.66	74.1	43.6	[33]
PCT	88	80	0.87	95	57	[33, 34]
sRAGE	75	85	—	—	—	[35, 36]

Table 1.
Biomarkers and their predictive parameters in sepsis.

Several studies have shown that PCT’s serum levels may be a guide in antibiotic therapy and can also be used to safely reduce the excessive exposure of these patients to drugs, thus reducing the adverse effects of sepsis treatment and avoiding the development of multiresistant bacteria [20].

Considering several studies cited in this chapter, the sepsis survival campaign published in 2017 suggested that the PCT monitoring should be used to verify the dosage and duration of antimicrobial treatment in patients with sepsis [32].

In **Table 1**, we summarize some parameters that reveal the predictive potential of the biomarkers mentioned above. Among them, we emphasize the sensitivity and specificity of each biomarker demonstrated by the ROC curve. The area under the ROC curve (AUC) represents the performance of the biomarker. We also specified in the table the positive and negative predictive values for each marker.

3. Promising biomarkers

3.1 Receptor for advanced glycation end products

The receptor for advanced glycation end products (RAGE) recipient is a standard recognition receptor that participates in a wide variety of physiological and pathological processes, such as diabetic complications, cancer, atherosclerosis, and inflammation.

The studies that relate soluble RAGE (sRAGE), the extracellular domain of RAGE, to the sepsis are very recent since even the discovery of this receptor’s soluble form occurred in 2009 [37]. It has been reported that an increase in the level of sRAGE would be a protective mechanism since its presence in plasma contributes to the removal or neutralization of ligands for RAGE, thus acting as a “false” receptor [38]. However, Wang et al. [39] reported a deletion effect of sRAGE in the inflammatory process, since it would bind to CD11b receptors of leukocytes, thus propagating inflammation.

Based on these contradictory results in scientific literature, in 2014, our group published a study demonstrating a positive correlation between serum levels of sRAGE with IFN- γ in patients with sepsis. We also observed significant correlations between levels of IL-1 α , IL-6, IL-8, IL-10, and IP-10 and sRAGE in patients with septic shock. We concluded that sRAGE blood levels may be associated with the mortality of patients with septic shock [35].

Further studies support this assertion, such as the study by Matsumoto et al. [40] demonstrated that the sRAGE serum level of patients with sepsis increases directly proportional to the severity of the disease, suggesting that sRAGE reflects on the RAGE’s signaling pathway inducing an excessive inflammatory response involved in endothelial injury and coagulopathy.

In the same year, Wang et al. [41] demonstrated that the decrease in sRAGE levels in mice results in improved sepsis-induced lung damage, thus decreasing mortality in this condition. Another study by Narvaez-Rivera et al. [36] demonstrated in 2015 that sRAGE's level in the plasma is high in patients with community-acquired pneumonia associated with sepsis and is also an independent factor for the likelihood of a fatal outcome.

Further studies are still needed to elucidate the mechanism of action of sRAGE in sepsis and septic shock; however, this receptor appears to be a promising biological marker for sepsis.

3.2 Nitric oxide

Nitric oxide (NO) is a highly reactive soluble gas that is endogenously synthesized by the three isoforms of the nitric oxide synthase enzyme (NOS), neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3). These molecules are known to be highly involved in cardiovascular homeostasis, so recent research has focused on its action on sepsis-induced heart disease [42].

In 2014, Nardi et al. [43] showed an increased NOS1 expression in vascular tissues in the sepsis condition, suggesting that this molecule could be a way to justify vascular dysfunction induced by the disease. This study suggests that the inhibition of this isoform may be an alternative to restore the effectiveness of vasopressors in later cases of sepsis.

In the same year, Martin et al. reported an association between NOS2 and NOS3 with sepsis. In the study, the authors suggest that this association could be related to the high level of NO in the blood plasma, which could consequently induce a failure of hemodynamics and increase the mortality of septic patients [44].

More recently, the critical care department of the First People's Hospital in Chun'an (China) demonstrated that monitoring changes in NO serum and amyloid A levels can be an efficient tool for defining patient prognosis and, when compared with CRP, would present better clinical results [45]. Despite the positive results on the use of nitric oxide as a biological marker for sepsis, many studies are still needed to fully understand its role in this condition.

3.3 Haptoglobin

Haptoglobin (Hp) is a protein whose main biological function is to bind free hemoglobin (Hb) and to prevent the loss of iron and subsequent kidney damage following intravascular hemolysis. When red cells are lysed, Hb binds to circulating Hp forming the Hp-Hb complex, which is then degraded by the reticuloendothelial system [46].

Although it is recognized that Hp is predominantly synthesized in the liver, studies reveal the expression of this protein also in other parts of the body, such as the lung, kidneys, heart, spleen, thymus, and brain [47–49]. There are reports that Hp levels are influenced by the acute inflammatory process and that such protein exerts an important antimicrobial and antioxidant function [50–52].

It is known that some patients with sepsis present deformity of hemoglobins, thus causing lysis of these cells and releasing them into the circulation [53]. In this context, the decrease in blood levels of Hp has already been described as a factor linked to increased mortality in patients diagnosed with sepsis, and, in animal models of sepsis, Hp supplementation has been shown to be able to decrease biomarkers of acute systemic inflammation [54, 55].

Even with this result, prospective and randomized studies are still needed to better elucidate the potential protective effects of endogenous and exogenous haptoglobin against the deleterious effects of free hemoglobin in septic patients.

3.4 Cytokines as biomarkers

Sepsis is characterized by two phases: a period of hyperinflammation, where the innate immune system is overactivated leading to production of proinflammatory cytokines such as TNF, IL-1b, IL-6, and IL8, and another period of immunosuppression where both adaptive and innate immunity are acting [56]. Clinical trials in septic patients showed an increase in the above-mentioned pro-inflammatory cytokines [57, 58].

However, contradictory results have been obtained for TNF and IL-1b. For example, the treatment of septic patients with anti-TNF antibodies did not affect the clinical outcome of patients [59]. In addition, these cytokines are not altered only in sepsis, after surgery or in autoimmune disease they are also altered and therefore are not specific.

On the other hand, studies have reported that IL-6 shows great promise as a biomarker [60–63]. Like TNF and IL-1b, IL-6 is not altered only in sepsis; nevertheless, several studies have shown its importance in the prognosis of sepsis presenting strong correlations with patient mortality [62, 63]. These results were also shown in an animal model of acute septic peritonitis (CLP) [61]. In this way, IL6 levels can show which patients may develop severe sepsis, and this reflects on possible interventions. Like IL6, IL8 has also been mentioned as a prognostic biomarker in septic patients especially in the early stages of the disease [64].

In the immunosuppression stage, IL-10 plays a key role in development of CARS trying to reduce hyperinflammation [65]. Therefore, studies have shown that high levels of IL-10 are correlated with a worse outcome and death [65–67]. In neonatal sepsis, IL-10 also proved to be an accurate biomarker. **Figure 1** illustrates the model proposed by van der Poll and van Deventer [68], emphasizing that the development of CARS still occurs in the pro-inflammatory phase of the disease. Thus, the mortality observed in the early stages of sepsis may be related to the hyper-inflammatory phase, and the late-stage deaths are related to the immunosuppressive phase as well as to secondary infections [56].

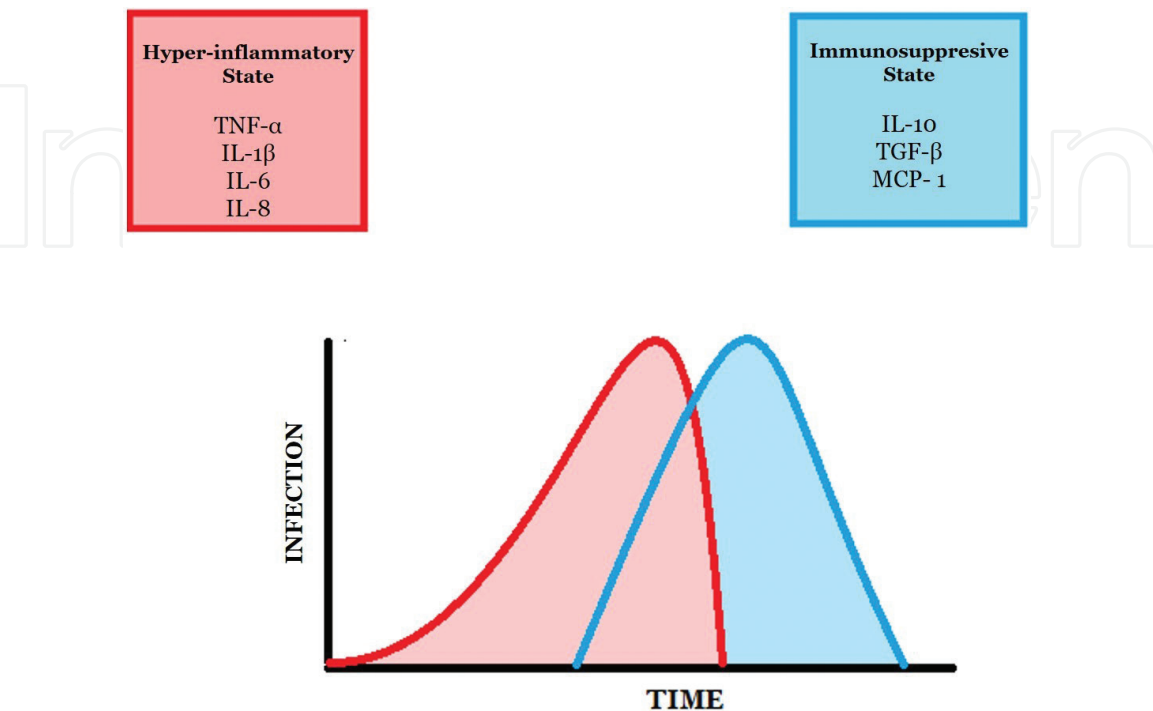


Figure 1.
Stages of sepsis and cytokine profile.

Accordingly, the cytokine profile in the septic patient could provide information about the stage of the disease and the patient's prognosis, contributing to a better intervention. In addition, we currently have a multiplex assay that simultaneously measures multiple cytokines with small plasma samples; however, this information should be interpreted with caution since the dosages of some cytokines in septic patients appear unclear in the literature needing to be standardized. Once standardized, the multiplex assay may be useful in the clinic.

3.5 Biomarker combinations

As previously seen, no biomarker has 100% sensitivity or specificity capable of predicting the clinical outcome for the patient with sepsis. Studies have shown that combining biomarkers may facilitate diagnosis and predict the outcome more faithfully.

As above mentioned, Guo demonstrated that the combination among lactate, CRP and BNP, or NT-proBNP has greater specificity for prognosis than isolated lactate dosage, being 100 and 69.23%, respectively [15]. Yu and colleagues [45] also showed that combining NO with SAA is an important tool to improve the prognosis of septic patients.

Clinical scores are not effective in early identification of infection in critically ill patients; however, combining these scores with biomarkers allows an early and accurate identification of sepsis. For example, Yoo and co-workers found that combining Modified Early Warning Score (MEWS), a tool for monitoring sepsis, with blood lactate levels was efficient for early identification of the disease [69]. The same was found by Bozza et al. [70] and Oberholzer et al. [71] when they combined the levels of MPC-1 or IL-6 with APACHE II, respectively, and found greater accuracy in the prognosis of the patients.

Other biomarkers aforementioned are also more accurate when combined. Han et al. showed that the association with CRP and PCT is an important tool to differentiate bacterial sepsis from other possible types of infection in critically ill patients [72]. Angeletti et al. [73] also showed that the combination among PCT, Tumor Necrosis Factor- α (TNF- α), and the adrenomedullin hormone fragment may help in the prior diagnosis and prognosis of septic patients, thus optimizing treatment of patients.

As mentioned above, IL-6, IL10, and IL-8 cytokines may also be altered in septic patients. In this way, combining cytokine dosage with another biomarker may improve the diagnosis. For example, it has been shown that combining CRP dosage with IL8 and IL2 was useful in the diagnosis of neonatal sepsis [74]. Another study with adult septic patients measured TNF, IL6, and IL10 and demonstrated that combining IL6 (pro-inflammatory) with IL10 (anti-inflammatory) cytokines was useful in establishing the prognosis. Moreover, high levels of IL-6 and IL-10 were related to high patient mortality [75].

Another combination has been demonstrated by Wong and colleagues who showed that interleukin-27 (IL-27) when combined with PCT can improve the diagnostic accuracy in septic patients when compared to each biomarker alone [76]. In 2012, Andaluz-Ojeda et al. [66] using the multiplex assay demonstrated that combining pro—IL-6 and IL-8—and anti-inflammatory cytokine—IL10 and MCP-1—levels was more predictive than analyzing each cytokine separately. Furthermore, high levels of these cytokines were positively correlated with the patient's mortality rate.

4. Conclusion

In this chapter we have outlined some biological markers established in the literature and that have recognized clinical relevance for sepsis, such as CRP [18],

lactate [11], BNP [24], and procalcitonin [28]. In addition, we also present some biomarkers that we believe are promising for the disease (sRAGE, NO, and haptoglobin).

The choice of the promising biomarkers cited in this chapter considered the clinical relevance of each of them (demonstrated by several studies) and our experience in the field. However, we recognize that there is a broad spectrum of quality papers published in the area of biomarkers for sepsis and that unfortunately those were not mentioned in this chapter.

Among the new research targets, we believe that sRAGE may be one of the most promising ones in severe sepsis. Our group demonstrated that this soluble receptor can be used as a tool to define the death prognosis of patients with septic shock, presenting a sensitivity of 75% and specificity of 85% [35].

In conclusion, it is noticeable that the currently used methods, even effective ones, require optimization. In this sense, one of the alternatives is combining biological markers, such as those exposed in this chapter, in order to increase the sensitivity and specificity of the diagnosis and prognosis of patients with sepsis, so that the treatment of this disease is increasingly early and efficient.

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