INTRODUCTION

The word sepsis originates from the Greek word \([\sigma\epsilon\pi\varsigma]\), which refers to bacterial decomposition of animal- or plant-based organic materials (Geroulanos & Douka, 2006). In addition to that, it was also mentioned by Homer’s poems as “sepo” \([\sigma\epsilon\pi\omega]\), by which he meant “I rotted.” Even during the 460–370 BC, Hippocrates, in order to describe “dissolution of a structure,” used the word “sepidon” which is synonymous with modern-day sepsis. Interestingly, the term was also used by great philosophers and physicians like Aristotle and Galen with similar meaning and prevailed for over 2,700 years (Gül, Arslantaş, Cinel, & Kumar, 2017). However, it was not until the ACCP/SCCM Consensus Conference in Chicago in 1991 that the terms related to sepsis were standardized (Bone et al., 1992). The conference aimed at providing general guidelines for future investigations related to sepsis, so that researchers could compare and improve various existing therapeutic protocols. They provided a definition of sepsis and systemic inflammatory response syndrome (SIRS) along with details of physiological parameters which can categorize sepsis and non-sepsis cases. In modern medical science, sepsis can be broadly defined as an unbalanced immune response of an organism to an infection that eventually ends up injuring its own organs or tissues. However, the definition of sepsis has changed over the years. Due to advancement in science and technology, now it is possible to assess sepsis criterion based on patient’s past health records data. Thus, the definition was modified in 2001, and again on 2016, the latest definition of sepsis has been provided by a task force comprising of personnel from infectious diseases, intensive care unit (ICU) and surgical and pulmonary specialists. They have published their recommendations in The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), where sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Also, SIRS was substituted with a shortened sequential organ failure assessment score known as the quick Sequential Organ Failure Assessment (qSOFA) score. This comprises of two of the following three physiological conditions suffered by a patient: increased breathing rate, low blood pressure and change in level of consciousness (Singer et al., 2016). Based on historical records on the inception and expression of sepsis, Figure 1 illustrates the transformation of sepsis definition over a span of 24 years.

Sepsis starts with an inflammatory response to the presence or invasion of a microorganism. Several clinical symptoms arise with the progression of sepsis, including a rise in body temperature above $38.3^\circ C (101^\circ F)$ or a temperature drop below $36^\circ C (96.8^\circ F)$,
a heart rate and respiratory rate of more than 90 beats/min and 20 breaths/min, respectively, acute alternations in white blood cell (WBC) count, that is either > 12,000 per cu. mm. or < 4,000 per cu. mm. Sepsis can progress towards severe sepsis resulting in multiple organ dysfunctions. Further on, a host can suffer from septic shock which is accompanied by hypotension despite adequate fluid resuscitation and perfusion abnormalities including lactic acidosis, oliguria or an acute alteration in mental status (Bone et al., 1992).

More than 1. million cases of sepsis are registered in the United States each year and approximately 270,000 result in death. Moreover, 1 in 3 deaths that occur in hospitals is due to sepsis. Sepsis occurs unpredictably and progresses alarmingly fast. Septic shock, a widespread inflammation all over the body ultimately leading to multiple organ failures and deaths, sets in if sepsis is not detected at an early stage. Therefore, understanding the symptoms and early diagnosis of sepsis is of utmost importance Thompson, Venkatesh, and Finfer (2019) and Gyawali, Ramakrishna, and Dhamoon (2019) has narrated a comprehensive review on sepsis, its physio-pathogenesis, along with the current optimal approach in managing the physiological conditions in human being relating to sepsis.

This review paper compliments the survey published by Berg and Gerlach (2018), Kumar, Tripathy, Jyoti, and Singh (2019), Polat, Ugan, Cadirci, and Halici (2017), Rello, Valenzuela-Sanchez, Ruiz-Rodriguez, and Moyano (2017) and Wentowski, Mewada, and Nielsen (2019) on recent advancement of sepsis, management and its diagnosis methodologies. This article puts an extra layer on top of existing surveys which includes the recent advancements in sepsis diagnostic techniques and methodologies explored in the year 2019. Along with that care has been taken to include the most popular sepsis diagnosis techniques over the years and they are grouped by their detection principle and depicted in form of tables. Amendments to these techniques should lead to the fabrication of point-of-care devices which would result in early and quick diagnosis of sepsis and eventually save more lives in ICU by exercising proper antibiotics early on. The main focus of this survey paper is the review of causes of sepsis, molecular mechanisms underlying sepsis, and labelled and label-free sepsis diagnostic systems along with their advantages and limitations. Finally, the article ends with a discussion on the future prospects of diagnosis and treatment of sepsis.

2 | CAUSES AND EFFECTS OF SEPSIS

2.1 | What underlies sepsis?

In the past years, several researches have been conducted to understand the root cause of sepsis, for example Hotchkiss et al. (2016), Schouten, Wiersinga, Levi, and Van Der Poll (2008) and Ward and Bosmann (2012). From prevalent research, it is understood that the severity resulting from sepsis is not directly caused by invading microorganisms or pathogens; rather, this clinical condition is caused by dysregulation of the host immune response that leads to multiple organ dysfunction, coagulopathy and hypotension (Schouten et al., 2008). This requires understanding of the interrelation between infection, inflammation and coagulation as well as the difference between immune response during regular infection and during sepsis. In Opal and Esmon (2002), authors have claimed that when an external pathogen invades, an attempt is made by the host defense system to prevent the foreign organisms from spreading and multiplying inside the host body. This event is thus followed by an inflammatory response that activates the coagulation process and fibrin deposition. However, the exaggerated response of the immune system leads to a situation where severe coagulation leads to
microvascular thrombosis and organ dysfunction also known as disseminated intravascular coagulation (DIC) (Levi & Ten Cate, 1999).

Essentially, this microvascular thrombosis is an adaptive response of the immune system when there is an infection that prevents the intruding pathogens present in the tissues from entering the systemic circulatory system. Thus, by clotting the path between the tissue and circulatory system temporarily, the immune system with the help of natural killer cells (a type of white blood cells) removes the pathogens or bacteria and repairs the damaged tissues. However, during acute infection, the microvascular thrombosis becomes generalized, which results in organ failure and eventually death due to extensive tissue ischaemia (i.e. inadequate blood supply to an organ).

This phenomenon is supported by studies on post-mortem of patients found positive with sepsis, as they demonstrate microvascular thrombosis in many organs including the lung, adrenals, liver, gut, kidney and brain (Dixon, 2004). Researchers therefore have found a relation between inflammation and coagulatory response in the host system (Esmon, 2005; Levi, van der Poll, & Buller, 2004) and have acknowledged the significance of endothelial activation for microvascular dysfunction, which is one of the hallmarks of sepsis (Aird, 2003; Bateman, Sharpe, & Ellis, 2003).

2.2 | Compromise of immunity by sepsis

One aspect of immunity is the viable lymphocytes, a subtype of WBC, which mainly comprises of natural killer (NK) cells (Freud, Mundy-Bosse, Yu, & Caligiuri, 2017), T cells (thymus) (Kumar, Connors, & Farber, 2018) and B cells (bone marrow) (Cooper, 2015). NK cells are generally part of the innate or inborn immune system and are best known for killing the tumours and virally infected cells. On the other hand, T cells are involved in cell-mediated immunity; that is, they provide immunity by activating phagocytes, antigen-specific cytotoxic T lymphocytes and release multiple cytokines in response to a foreign organism (also called antigen). B cells respond to pathogens by generating large amount of antibodies for neutralizing these foreign bodies, for example bacteria and viruses. These lymphocytes along with dendritic cells (DCs) (Luckashenak & Eisenlohr, 2013) can become dysfunctional during sepsis.

A recent study Boomer et al. (2011) infers that during sepsis there is a massive apoptosis of T and B cells which is accompanied by profound immunosuppression. An increased number of T suppressor cells are also noted. Sepsis can turn out to be lethal with the apoptosis of T and B cells followed by defective DCs and marks the onset of immunosuppression. As a result of this defective innate immune system, the ability to engulf bacteria is greatly reduced, resulting in multi-organ failure (MOF) and finally death. Studies also reveal that sepsis can result in a huge build-up of reactive oxygen species (ROS) which causes redox imbalance in WBCs (leucocytes) and organs. This increased number of ROS and WBC imbalance gives rise to an inflammatory response called systemic immune response syndrome (SIRS), along with a sustained immune response and other immune activation states in endothelial cells and leucocytes that ultimately causes MOF and death. The detailed analysis and pathways are narrated in several papers including Budd (2002), Hotchkiss et al. (2001, 2016), Kasten et al. (2010), Peck-Palmer et al. (2008) and Riedemann et al. (2002).

3 | MOLECULAR MECHANISMS IN SEPSIS PATHOGENESIS

Any severe insult to the body including burns, pathogen attacks or severe surgeries triggers inflammatory responses by releasing one of the two types of molecular patterns into the bloodstream: damage-associated molecular patterns (DAMPs), when the body suffers from an injury, or pathogen-associated molecular patterns (PAMPs), when a pathogen invades the body (Bone, 1996). In order to understand the complex flow of events that accompanies sepsis, let us consider the example of bacterial infection. In this section, the flow of events, that is the immune response of the body that follows the inception of bacterial infection, is narrated to facilitate easy grasp of the complex biological phenomenon. (The flow of events associated with the immune response of the body is nearly similar for most of the infections or injuries.)

Bacterial cell walls are composed of lipopolysaccharides (LPSs) which are also known as endotoxin. These toxin molecular patterns that are present inside a bacterial cell are released when the cell disintegrates. These patterns are known as PAMPs and are received by Toll-like receptors (TLR) that reside on the host cell surface. TLRs belong to a class of proteins usually expressed on the leucocyte membranes including macrophages, dendritic cells and cells of adaptive immunity (T and B lymphocytes) that recognize molecules derived from pathogen. This binding between LPS and TLR releases pro-inflammatory cytokines including tumour necrosis factor α (TNFa), interleukins (IL-1β, IL-6, IL-12), macrophage inflammatory protein-1α (MIP-1α), and human leucocyte antigen (HLA) that encodes the major histocompatibility complex (MHC) proteins in human being, as illustrated in Figure 3a (Jaffer, Wade, & Gourlay, 2010). Release of these cytokines is followed by a cascade of other inflammatory chemokines such as IL-8 and C–C motif ligand 2 (CCL2), also known as monocyte chemotactic protein-1 (MCP-1) (Bone et al., 2015).

Figure 2 illustrates the immune response resulting from bacterial infection that initiates the following two processes:

- Recognition of multiple infection-derived microbial products (Hotchkiss et al., 2016), and
- Signalling the specific cell surface receptors on cells (immune, epithelial and endothelial), whose primary job is to continuously sample their local environment and do surveillance (Takeuchi & Akira, 2010).

C-reactive protein (CRP) is another protein, synthesized by the liver and found in blood plasma, whose circulating concentrations increase following IL-6 secretion by macrophages and T cells (Sproston & Ashworth, 2018). Procalcitonin (PCT) is also produced by
many cells in the body in response to both the infection and injuries. These phenomena are known as *systemic immune response syndrome* (SIRS) that leads to inflammation and coagulation.

Almost simultaneously, an anti-inflammatory response called *compensatory anti-inflammatory response syndrome* (CARS) is triggered in the body that strives to compensate the inflammatory process. This generates anti-inflammatory cytokines such as IL-4, IL-10, IL-11 and IL-13 (Zhang & An, 2007). These cytokines inhibit pro-inflammatory cytokine synthesis. Hence, in general, with the invasion of any infection this complex dyad of inflammation and coagulation occurs with a balance between SIRS and CARS. The balance is disturbed when CARS does not kick in at the right time and instead of activation of T cells by macrophages, apoptosis of T cells occurs, as shown in Figures 2 and 3b.

HLA-DR expression on macrophages is also reduced in patients suffering from severe sepsis. HLA-DR is an MHC class II cell surface
receptor that resides on antigen-presenting cells, that is macrophages, B cells and dendritic cells. The prime role of HLA-DR is to present peptide antigens, originating from the bacterial cells, to T cell receptors (TCRs) residing on T cells. This eventually produces antibodies against the peptide antigen. However, in the event of severe sepsis, reduced expression of HLA-DR is also accompanied by an increased expression of the negative co-stimulatory molecule CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) (Roger et al., 2009) as well as another molecule associated with apoptosis of T cells called PD-1 (programmed cell death) (Zhang et al., 2011). Generally, T cells express a positive co-stimulatory molecule called CD28. Along with the TCRs, it recognizes peptide antigens presented by macrophages, which activates the T cell. However, reduced expression of CD28 and enhanced expression of the alternative ligand CTLA-4 (also called CD152) leads to apoptosis of T cells (Kessel, Bamberger, Masalha, & Toubi, 2009). When there is a lack of T cells, the production of antibodies against the bacterial peptide antigen is reduced, thus delaying the elimination of bacterial infection. This leads to prolonged coagulation (one which tries to prevent the migration of infection to various organs of the body), and eventually due to this delayed coagulation, there is an insufficient supply of blood and nutrients to the organs which leads to organ failure and tissue toxicity. This becomes the cause of fatality in sepsis patients.

4 | IMPACT STATISTICS OF SEPSIS

In order to appreciate the impact of sepsis worldwide, we hereby present a statistical representation of the scenario. Among the reported cases, there are over 31.5 million people who develop sepsis each year worldwide. Among those, 19.4 million suffer from severe sepsis and about 5.3 million people die (Fleischmann et al., 2016). Further, it has been estimated that there are about 3 million cases of sepsis in neonates and 1.2 million in children per year globally, with mortality rates between 11% and 19% (Fleischmann-Struzek et al., 2018). Due to puerperal sepsis, about 75,000 women die every year around the globe (Dillen, Zwart, Schutte, & van Roosmalen, 2010). With mortality rates between 28% and 50% (Gaieski, Edwards, Kallan, & Carr, 2013), sepsis is clearly lethal; it also is remarkably expensive to treat. It is considered as one of the most exorbitant conditions to treat in the hospitals and clinics in the United States, wherein the average cost for treating 3.1 million population sums up to US $4 billion per year (Gaieski et al., 2013; Lagu et al., 2012). The estimated number of deaths in the United States due to sepsis is higher than the combined deaths from prostate cancer, AIDS and breast cancer (Adhikari, Fowler, Bhagwanjee, & Rubenfeld, 2010).

A statistical overview and comparison among infectious diseases and mortality rates are illustrated in Figure 4. Underlying these stern numbers, a key factor is the absence of an accurate, prompt and point-of-care (POC) sepsis diagnostic method (Daniels, 2011). Early detection of the onset of sepsis is critical since for every hour of delay in exercising an appropriate antimicrobial medication to the patients’ results in roughly 7.6% decrease in survival rate. Mortality rates for each hour of antibiotic delay
are shown in Figure 5 (Linnér et al., 2013). The surviving patients who get discharged still suffer from a continuing risk of mortality (Hotchkiss et al., 2000).

These warrant an urgent need for an early detection of sepsis (Kumar et al., 2006). In addition, a general awareness also needs to be instilled into the people and authorities. With this perspective, World Sepsis Day is observed across the globe since 2012 on 13 September every year. Statistical analysis of Google search data on sepsis worldwide depicts a considerable amount of rising awareness regarding sepsis among the world population as illustrated in Figure 6b. However, as the treatment of sepsis is considerably expensive, majority of sepsis trials registered at ClinicalTrials.gov (the US clinical trials registry, which is the largest in the world) and anzctr.org.au (the Australian New Zealand Clinical Trials Registry) belong to high-income countries as shown in Figure 6a (Rudd et al., 2018). Therefore, clinicians and engineers are striving towards developing novel techniques and devices for fast and accurate diagnosis of sepsis.

5 | TRADITIONAL SEPSIS DIAGNOSTICS

Diagnosis of sepsis by traditional methods includes blood, urine, cerebrospinal fluid (CSF) and bronchial fluid culture. Generally, CRP or leucocyte count acts as an indicator or clinical sign for sepsis. Blood cultures are performed in continuous monitoring blood culture systems (CMBCS) and follow a set of pre-approved guidelines (Wilson, 2007).

Fully automated systems are prevalent for incubating the blood samples along with detection and analysis of CO₂ released and O₂ exhausted during the culture process. The sensing is generally performed using fluorescent sensors, which are popularly known as

![Figure 6](image_url) (a) Sepsis trials are predominantly conducted in high-income countries (Rudd et al., 2018); (b) rise in awareness worldwide (Savelkoel, Claushuis, van Engelen, Scheres, & Wiersinga, 2018)

![Figure 7](image_url) Conventional labelled detection technology: (a) FRET; (b) ELISA
| Device          | Company                 | Detection method          | Sample            | Time-to-detect | Diagnosis          | FDA approved | POC |
|-----------------|-------------------------|---------------------------|-------------------|----------------|--------------------|--------------|-----|
| EPOC            | Siemens                 | Blood gas (analyser)      | Whole blood       | 1 min          | qSOFA              | Yes          | Semi |
| i-STAT          | Abbott                  | Immuno-analysers          | Whole blood       | 30 min         | Circulating proteins | Yes          | Yes |
| SepiFast        | Roche                   | PCR                       | Whole blood       | 6 hr           | Identify pathogens | Yes          | No  |
| FAST-ID BSI Panel | Qvella              | PCR                       | Whole blood       | 1 hr           | Identify pathogens | Yes          | No  |
| Microbiology–Septi-Chek | Becton Dickinson | Blood culture             | Whole blood       | 38 hr          | Identify pathogens | Yes          | No  |
| Oxoid Signal    | ThermoFisher Scientific | Blood culture            | Whole blood       | 24 hr          | Identify pathogens | Yes          | No  |
| QuickFISH       | AdvanDx                 | Fluorescence/Flow cytometry | Positive blood culture | 1–2 hr     | Cell antigen expression | No          | No  |
| Accllix         | LeukoDx                 | PCR                       | Positive blood culture | 1–2 hr     | Identify pathogens | Yes          | No  |
| Sepsitest       | Molzym                  | PCR/DNA Amplification     | Whole blood       | 1–2 hr         | Identify pathogens | Yes          | No  |
| AST             | ImpeDx                  | Microfluidics/Electrochemical | Positive blood culture | 1–5 days | Identify pathogens | Yes          | No  |
| hemoFISH        | Miacom Diagnostics      | Fluorescence              | Positive blood culture | 0.5 hr     | Identify pathogens | Yes          | No  |
| Verigene        | Luminex                 | PCR                       | Positive blood culture | 3.5 hr    | Identify pathogens | No           | No  |
| FilmArray       | Biofire Diagnostics     | PCR                       | Positive blood culture | 3 hr       | Identify pathogens | No           | No  |
| HYPLEX          | BAG                     | PCR                       | Positive blood culture | 3 hr       | Identify pathogens | No           | No  |
| ACCU-PROBE      | Gen-probe               | Chemi-luminescent         | Positive blood culture | 3 hr       | Identify pathogens | Yes          | No  |
| PLEX-ID BAC     | Abbott                  | PCR                       | Positive blood culture | 6 hr       | Identify pathogens | No           | No  |
| Staph SR        | Becton Dickinson        | PCR                       | Positive blood culture | 3 hr       | Identify pathogens | Yes          | No  |
| StaphPlex       | Qiagen                  | PCR                       | Positive blood culture | 5 hr       | Identify pathogens | No           | No  |
| MALDI-TOF       | bioMerieux              | Matrix assisted Laser desorption | Positive blood culture | 2 hr     | Identify pathogens | No           | No  |
| Magicplex       | Seegene                 | PCR                       | Whole blood       | 3.5 hr         | Identify pathogens | No           | No  |
labelled sensing techniques (Łakowicz, 1999). Figure 7 illustrates two such common labelled techniques known as fluorescence resonance energy transfer (FRET) (Ranjan, Esimbekova, & Kratasyuk, 2017) and enzyme-linked immunosorbent assay (ELISA) (Voller, Bartlett, & Bidwell, 1978) for detecting biomarker proteins. In addition to the labelled sensing techniques, there are several other techniques to estimate the concentration of gases released—calorimetric analysis (Jin, Moon, & Kwak, 2016), automated growth detection techniques and hybrid techniques including—lysis centrifugation-intrinsic fluorescence method (LC-IF), intrinsic fluorescence method for fast and direct identification of pathogens in blood cultures (Walsh et al., 2013). There are some relatively new detection schemes that include—multiplexed polymerase chain reaction (PCR) + hybridization or microarray, PCR + mass spectroscopy, broad-spectrum PCR. These are primarily exercised on whole blood. Also, specialized techniques are employed nowadays for identification and susceptibility testing of positive blood culture. Use of techniques such as matrix-associated laser desorption ionization–time of flight (MALDI-TOF), molecular point-of-care test (POCT) and their combination or multiplexed PCR along with mass spectroscopy are employed to increase the accuracy in the quantification of the pathogens. Most recent research published in late 2019 by Trung, Thau, Bang, and Song (2019) bolsters the findings on PCR’s supremacy over conventional blood culture-based gold standard. They have demonstrated that their Sepsis@Quick test is much faster in detecting poly-microbial infections and multiple numbers of pathogens at a time.

Table 1 summarizes the conventional techniques for sepsis detection that rely mostly on pathogen detection (20 techniques are reported) (Oeschger, McCloskey, Kopparthy, Singh, & Erickson, 2019; Reddy et al., 2018). A schematic diagram comparing the conventional and recent diagnostic methods for sepsis is depicted in Figure 8 (Cohen et al., 2015). These methods involving analysis of blood culture is currently the gold standard for detecting any infectious disease such as sepsis. However, there are several limitations associated with the traditional diagnostic methods (Mancini et al., 2010) which are briefly discussed in the next section.

5.1 Limitations of traditional sepsis diagnosis systems

The limitations associated with traditional sepsis diagnosis systems are listed below:

- **Prolonged testing time**: Blood culture tests take about 24–72 hr to confirm the prevalence of infection, pathogen invasion and antimicrobial susceptibilities (Beekmann, Diekema, Chapin, & Doern, 2003; Campbell, Marrie, Anstey, Dickinson, & Ackroyd-Stolarz, 2003; Campbell, Marrie, Anstey, Dickinson, & Ackroyd-Stolarz, 2003), and by the time a positive result arrives, the patient may have started suffering from severe sepsis or septic shock along with multiple organ failure.

- **Miss-classification due to non-specificity**: The anomalous counts for leucocytes or CRP may be misleading as that might be an outcome of some other clinical conditions or diseases rather than sepsis, thereby increasing the false-negative rate (Angus & Van der Poll, 2013).

- **Blood volume required for culture**: Studies reported at (Bouza, Sousa, Rodríguez-Créixems, Lechuz, & Munoz, 2007; Connell, Rele, Cowley, Buttery, & Curtis, 2007) confirm that the diagnostic yield improves with increase in extracted blood volume. Moreover, insufficient blood volume often yields in false-negative results. However, extracting large volume of blood from neonates and other paediatric patients with certain critical clinical conditions is not always possible. This can be a bottleneck of traditional blood culture methodologies.

- **Existence of slow-growing pathogens**: Some pathogens multiply and express themselves slowly and this results in low microbial activities in the culture media, which reduces the signal-to-noise ratio.
Sepsis diagnostic methods are of paramount significance. Conventional blood culture-based sepsis diagnosis, and hence, less limiting inflammatory responses for different patients, distinguishing sepsis concentration of biomarkers correlates well with the severity of sepsis. Lipopolysaccharide (LPS) binding protein and CD64. Although concentrations of 'presepsin' (sCD14-ST), most common sepsis biomarkers—PCT, CRP, IL-6, soluble triggering receptor expressed on myeloid cells-1, and CRP and their clinically important concentrations (Reinhart, Bauer, Riedemann, & Hartog, 2012).

It is evident that several diagnostic dilemmas prevail in traditional blood culture-based sepsis diagnosis, and hence, less limiting sepsis diagnostic methods are of paramount significance.

### 6 | BIOMARKER-BASED LABEL-FREE SEPSIS DIAGNOSIS

The limitations of the traditional diagnosis discussed in the previous section motivate intervention of several inter-disciplinary techniques. In the past decades, many novel techniques have been developed with the aim to mitigate the existing limitations and achieve lower limits of detection. Some detection techniques focused on detecting the sepsis biomarker or a combination of biomarkers rather than directly detecting the pathogens, whereas some others studied the motion or motility of various blood components in a sepsis patient and compared those against a healthy individual. Biomarkers are measurable substances, the concentration of which increases or decreases in response to diseases, infections or other environmental factors. The level of a specific biomarker or a combination of biomarkers gives an indication of the presence of a medical condition or disease. A large number of sepsis-related biomarkers has been reported in literature. However, the accuracy and effectiveness of biomarker-based sepsis detection cannot be evaluated until and unless the results are compared to some standards. In Liu, Hou, Li, Kj, and Wang (2016), the authors conducted a systematic review and meta-analysis in order to evaluate the biomarkers reported in the last two decades by retrieving information from journals including PubMed and EMBASE. They identified seven most common sepsis biomarkers—PCT, CRP, IL-6, soluble triggering receptor expressed on myeloid cells-1, presepsin (sCD14-ST), lipopolysaccharide (LPS) binding protein and CD64. Although concentration of biomarkers correlates well with the severity of sepsis, due to the lack of specificity of biomarkers and different early inflammatory responses for different patients, distinguishing sepsis from other similar type of non-sepsis clinical conditions is critical.

According to PIERRAKOS AND VINCENZ (2010), approximately 178 sepsis biomarkers have been identified. But no biomarker shows sufficient sensitivity and specificity to sepsis (NOBRE, HARBARTH, GRAF, ROHRER, & PUGIN, 2008) with one exception of PCT (JONG ET AL., 2016; ROWLAND, HILLIARD, & BARLOW, 2015). Hence, a combination of biomarkers can lead to better specificity and sensitivity (VINCENZ & BEUMIER, 2013). Table 2 lists the three major sepsis-related biomarkers IL-6, PCT and CRP and their clinically important concentrations (Reinhart, Bauer, Riedemann, & Hartog, 2012).

In the following sub-section, we discuss some existing "label-free" sepsis detection schemes which ultimately may lead to a POC (point-of-care) solution to sepsis detection.

#### 6.1 | Electrochemical approach

Electrical transducers are widely used due to their high sensitivity, simplicity and amenability to inexpensive miniaturization. The increasing need for a patient-centred, efficient and inexpensive diagnostic system has resulted in the emergence and development of POC sepsis diagnostic systems. Min et al. (2018) reported the development of a POC platform, termed IBS (integrated biosensor for sepsis) for rapid and reliable sepsis identification. A portable platform comprising of a disposable kit (to capture sepsis biomarker interleukin-3 (IL-3) on magnetic beads and label it for subsequent electrochemical measurements), an electrical detection system (to measure electrical current for IL-3 quantification), a microcontroller unit for signal processing and a bluetooth module for wireless communication, all packaged into a single monolithic device, outperformed the conventional enzyme-linked immunosorbent assays (ELISA) by providing > 5 times faster response, >10 times more sensitivity and an order of magnitude larger dynamic detection range. Further, using human clinical samples \( n = 62 \), sensitivity and specificity of 91.3% and 82.4% were achieved, respectively. In addition, survival analysis on patients suffering from septic shock confirmed the significance of IL-3 as an indicator of organ failures. The total cost of the device was broken down to about $50 for the IBS reader and $5 per test for the reagent use. A scale-up production is expected to further reduce these prices, thus providing IBS competitive cost advantages over ELISA ($11) or lateral flow strips ($10–$20).

The limitations in differentiating sepsis from other non-infectious causes of SIRS are overcome through multiplexed detection of multiple biomarkers that results in improved diagnosis. In this regard, Selvam and Prasad (2017) reported the first-of-its-kind electrochemical impedance spectroscopy (EIS)-based nanochannel system built with a nanoporous nylon membrane integrated onto micro-electrodes. The covalent binding of biomarkers onto the electrode surface formed an electrical double layer which was transduced as impedance changes and recorded via EIS. The sensor was demonstrated to detect three sepsis biomarkers, PCT, LPS and lipoteichoic acid (LTA) in pooled human serum as well as in human whole-blood samples with LODs of 0.1 ng/ml, 1 µg/ml and 1 µg/ml respectively.

| Biomarker | Concentration in blood (normal) [pg/ml] | Concentration in blood (sepsis) [pg/ml] |
|-----------|----------------------------------------|----------------------------------------|
| CRP       | <3                                     | >3                                     |
| PCT       | <10                                    | 10–10,000                               |
| IL-6      | <1                                     | 1–5,000                                 |
Other electrochemical sensors using highly oriented pyrolytic graphite (Mahe, Green, Winlove, & Jenkins, 2014), host-guest nanonet electrode (Shen et al., 2015) and enzyme-conjugated acrylic microspheres and gold nanoparticles composite coated onto a carbon-paste screen printed electrode (Mansor et al., 2018) were also developed for sepsis biomarker detection as illustrated in Figure 9. Most recent development in electrochemical detection of sepsis in the year 2019 is the fabrication of needle-shaped microelectrodes which can detect the levels of IL-6 (Russell, Ward, et al., 2019), a sepsis biomarker. Figure 9a depicts the packaged device along with the needle-shaped electrode structure and fabrication steps. Hannah et al. (2019) have also proposed an electrochemical detection method using screen printed electrodes, which provides a rapid test for antimicrobial susceptibility. Figure 9b illustrates the schematic of the detection system.

A comparative summary of 7 electrochemical sensors for sepsis diagnosis, detailing the samples they use, the biomarkers they target, the interfaces they utilize, their linearity and LOD and their references, is presented in Table 3.

### 6.2 Optical approach

Driven by the need to conduct in situ measurements of sepsis, optical detection has proved to be an appealing platform. Zubiate, Zamarreno, Sanchez, Matias, and Arregui (2017) developed a high-sensitive CRP measurement technique utilizing the lossy mode resonance (LMR) of optical fibres. LMR corresponds to the coupling of core mode of the fibre to a lossy mode in a thin film. Arregui et al. (2014) also developed a similar fibre-optic sensor utilizing LMR. The experimental set-up is illustrated in Figure 10a. A side polished D-shaped fibre was coated by a thin indium tin-oxide film and subsequently functionalized with layers of CRP-selective aptamers. The shifts in LMR wavelength were tracked in response to different concentrations of CRP solutions ranging from 0.0625 to 1 mg/L. The fabricated sensor could detect the minimum CRP concentrations of 0.0625 mg/L which is far below the clinical threshold value of 1 mg/L, demonstrating its potential in clinical diagnosis of sepsis.

Surface plasmon resonance (SPR) is another promising label-free technique for selectively identifying sepsis. In Vance and Sandros (2014), an SPR system was developed to detect ultra-low concentrations of the CRP biomarker in blood. In this work, a sandwich assay was implemented by introducing aptamer-modified quantum dots (QDs), which could measure 7 zeptomole (at 5 fg/ml) of CRP in spiked human serum. Figure 10b,c illustrates the set-up. Wang et al. (2017) coated a thin gold film on the exposed region of the fibre core to excite the surface plasmon polaritons at the interface between the gold coating and the dielectric overlayer. Afterwards, the SPR sensor was modified with a polydopamine, followed by the immobilization of anti-CRP monoclonal antibodies. The shifts in the SPR dip appearing at the output signal were measured, and the sensitivity was observed to be 1.17 nm per μg/ml. The optimum binding time between the anti-CRP and CRP was observed to be 60 min which is far less than the conventional schemes. A point-of-care application for PCT quantification was proposed by Rascher et al. (2014) that worked on the principle of total internal reflection (TIRF). A comparative summary

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**Figure 9** Electrochemical sensing: (a) packaged device, (b) microneedle, (c) fabrication steps (Russell, Ward, et al., 2019) and (d) rapid detection using screen printed electrodes (Hannah et al., 2019)
of 9 optical sensors for sepsis diagnosis, detailing the samples they use, the biomarkers they target, the interfaces they utilize, their linearity and LOD, and their references, is presented in Table 4.

6.3 Microfluidic-based approach

Ellett et al., (2018) reported a novel sepsis diagnostic procedure where the motility of neutrophils present in blood was measured in a microfluidic assay. This device, as illustrated in Figure 11, required only a drop of diluted whole blood for diagnosis. Five motility parameters were studied, and a hybrid score was calculated to estimate the prevalence of sepsis. Supervised machine-learning algorithms were also applied to narrow down the total number of control parameters which increased the efficiency of the overall diagnosis process. The motility of neutrophils collected from sepsis patients exhibited higher motility compared with neutrophils collected from a healthy human being. The complete detection process took about 6 hr to complete which may be viewed as a limiting factor. Recently, researchers from MIT (Wu & Voldman, 2019) have developed a novel point-of-care microfluidic chip to detect sepsis in about 30 min. This biochip detects levels of IL-6, which is a sepsis biomarker from blood. The novelty lies in the fact that the detection is possible using only microlitres of blood rather than conventional millilitres and can replace bulky devices with similar detection performance.

A comparative summary of 4 sepsis sensors realized on a microfluidic platform, detailing the samples they use, the biomarkers they target, the interfaces they utilize, their linearity and LOD, and their references, is presented in Table 5.

6.4 Field-Effect Transistor-Based Approach

Field-effect transistors have been gaining more attention for infectious disease detection because of their low-voltage operation (<1V), inherent gain amplification, biocompatibility and miniaturization (Torsi, Magliulo, Manoli, & Palazzo, 2013). Seshadri, Manoli, Marra, et al. (2018) developed an electrolyte-gated organic field-effect transistor (EGOFET) for label-free detection of PCT biomarker. The corresponding schematic diagram and actual implementation are depicted in Figure 12a,b, respectively. Monoclonal antibodies were immobilized on the surface of a poly-3-hexylthiophene (P3HT) organic semiconductor (OSC) that formed the transistor electronic channel. The antibody immobilization and analyte receptor binding events induced distinct changes in the transistor figures of merit, namely, threshold voltage, drain current and carrier mobility. The antibody functionalized to the OSC channel induced alterations in transfer path of charge carrier which translated into changes in carrier mobility. On the other hand, the net negative charge on the target PCT acted as traps for holes induced in the OSC, eventually reducing the drain current and shifting the device threshold voltage. The reported EGOFET could detect PCT concentrations, ranging from 0.8 pM to 4.7 nM.
with a detection limit of 2.2 pM. Similar FET-based label-free sensing using aptamer and carbon nanotubes has also been explored to detect IgE by Khung and Narducci (2013). Figure 12c illustrates a generalized scheme for fabrication of such sensors, where underlying detection principle is similar to EGOFET discussed earlier. Recently, Macchia et al. (2019) has developed similar organic transistor for detection of c-reactive proteins at its physical limits, which is of course an improvement over existing organic FETs.

**TABLE 4** Survey on optical sensors for sepsis diagnosis

| Principle                          | Sample          | Biomarker     | Interface                                           | Linearity & LOD | References                        |
|-----------------------------------|-----------------|---------------|-----------------------------------------------------|-----------------|-----------------------------------|
| Nanoplasmonic                     | Buffer          | E.Coli (bacteria) | Bioprinted Microarray-based lens-free interferometer | Single bacterial cell in 40 min | Dey et al. (2018) |
| Optical fibre (LMR)               | Blood plasma    | CRP           | Core-cladding interface                             | 0.625–1 mg/ml   | Zubiate et al. (2017)             |
| Plasmonic (nanoparticles)         | Buffer          | CRP           | Digital biomarker detection in microarray (NP-enhanced gold nanohole arrays) | 27 pg/ml        | Belushkin, Yesilkoy, and Altug (2018) |
| Fibre-based immunosensor          | Buffer          | IL–6          | Florescent magnetic nanoparticles                   | 0.1 pg/ml       | Zhang, Liu, and Goldys (2018)    |
| SPR                               | Human serum     | Folic acid proteins | Graphene + folic acid                                | 5–500 fM        | He et al. (2016)     |
| SPR                               | Buffer          | PCT           | KOH-treated gold-coated SPR chip                    | 4.2 ng/ml       | Vashist, Saraswat, and Holthšfer (2012) |
| Florescence[FRET]                 | Buffer          | Folate receptor proteins | Ag nanocluster-coated DNA/SWCNTs                  | 0.1–3 ng/ml, 33 pg/ml | He et al. (2017) |
| Total internal reflection florescence (TIRF) | Serum and plasma | PCT, IL–6     | Microarray-based multiparameter immunofluorescence assays | IL–6:0.27 ng/ml in serum 0.77 ng/ml in plasma PCT: 0.37 ng/ml in serum 1 ng/ml in plasma | Rascher et al. (2014) |
A combined comparative summary of 2 sepsis sensors realized on a FET platform, along with the other two approaches discussed in the following, detailing the samples they use, the biomarkers they target, the interfaces they utilize, their linearity and LOD and their references, is presented in Table 6.

### 6.5 Machine learning-based approach

With the advent of data analytics and machine-learning (ML) algorithms, researchers now have another way of predicting sepsis by using a set of observations from past diagnosis and tests. For instance, logistic regression (LR), support vector machines (SVM) and logistic model trees (LMT) were used to predict the onset of sepsis from the vital signs and blood samples of adult patients at the ICU (Wang, Sun, et al., 2018). Wang, Wang, et al. (2018) used a “random forest-improved fruit-fly optimization algorithm-kernel”-based learning machine to effectively diagnose the sepsis. The model employed random forest algorithm that enhanced the diagnosis accuracy. It was concluded that there was an increase in the levels of acetic acid and a decrease in linoleic acid and cholesterol levels in sepsis patients.

Sepsis is prevalent in newborns which makes its early detection extremely important. In Hu, Lee, and Tan (2018), three physiological attributes (Lehman, Mark, & Nemati, 2018) were utilized to predict sepsis which included the following: heart rate, respiratory rate and blood oxygen saturation. The experienced paediatricians at the NICU of Monash Children Hospital utilized these variables to predict the onset of sepsis in preterm infants. Machine-learning algorithms including multilayer neural network (NN), logistic regression (LR), support vector machines (SVM) with Gaussian kernel and ensemble learning models, including Random Forest (RF) and gradient boosting decision tree (GBDT), were used, and from the results, it was evident that RF and GBDT outperformed LR, SVM and NN. Authors also claimed that the method could accurately predict the onset of sepsis 24 hr in advance. This provides clinicians ample opportunities to restrict the infection before it begins to cause harm to the newborn.

Nowadays, hospitals are employing artificial intelligence (AI) to monitor the onset of sepsis. Duke University Hospital has officially launched Sepsis Watch that identifies incipient sepsis cases and raises an alarm (Strickland, 2018). Several other deep learning (convolutional—long/short-term memory) (Lin et al., 2018; Saqib, Sha, & Wang, 2018)-based prediction algorithms are also presented.

![Image](https://example.com/figure11.png)

**Figure 11** Microfluidic device to estimate neutrophil motility from a drop of blood (Ellett et al., 2018). Reprinted with permission from Springer Nature.
in literature that predict sepsis with high efficiency. Recent temporal patterns (RTPs) used in conjunction with SVM classifier outperforms some other state-of-the-art machine-learning techniques (Khoshnevisan et al., 2018). Also, cloud-based systems have been proposed that work in conjunction with ML and AI. For example, GE Healthcare and Roche Diagnostics have partnered together to provide a cloud-based digital analytical tool to utilize the petabytes of patient data that is generated by hospitals yearly. Also, Faisal et al. (2019) have developed a computer model which defines a new score called computer-aided National Early Warning Score (cNEWS) which they claim to be more accurate than conventional qSOFA score and also easily integrable with existing analytics in hospitals. These data provide a clear picture about an overall involvement of machine learning and data analytics tools in health care.

### 6.6 Miscellaneous approaches

In addition to the above-mentioned techniques, there are other diagnostic schemes for cost-effective, timely and real-time detection of infections. Recently, for easy tunability properties of the porous silicon (PSI) (e.g. pore morphology, photonic properties, biocompatibility and surface chemistry), biosensors based on PSI are gaining popularity. Over years, the initial drawbacks on sensitivity caused due to limited diffusion of biomolecules inside PSI nanoparticles have been overcome: the technique reported in Mariani, Pino, Strambini, Tedeschi, and Barillaro (2016) depicts a 10,000-fold increased sensitivity while detecting 3.0 nM concentration of sepsis biomarker protein TNFα with an enhanced signal-to-noise ratio of 10.6. Arshavsky-Graham et al. (2017) reported a proof of concept on enhancing the sensitivity by means of on-chip protein pre-concentration using electrokinetic iso-tachophoresis (ITP) on porous silicon (PSI) biosensor. The detection was based on reflective interferometric Fourier transform spectroscopy (RIFTS) with a LoD of 7.5 nM. Similar PSI-based interferometric highly sensitive label-free detection of sepsis biomarker TNFα was also reported in (Mariani, Strambini, Tedeschi, & Barillaro, 2017), where interferogram average over wavelength (IAW) reflectance spectroscopy was used as the detection principle, and concentrations ranging from 3 to 390 nM were detected. In Terracciano et al. (2019), authors have presented the recent progress in the development of PSI optical aptasensors for bioengineering and biomedical applications, also discussing various PSI functionalization strategies along with techniques to improve the device performance in terms of sensitivity, response time and limit of detection (LOD).

Voltammetric diagnosis (Ly, Kim, Hong, Kim, & Lee, 2018) of E. coli carried out on blood plasma infected by sepsis is another scheme in use. In Henne, Doorneweerd, Lee, Low, and Savran (2006), researchers developed a gold-coated quartz crystal microbalance biosensor for the detection of folate binding protein (FBP), which is a biomarker for sepsis. A LoD of 30 nM was achieved for the sensor. Figure 13a,b depicts the working principle of this acoustic biosensor for the detection of FBP. Figure 13c illustrates a generalized response curve for the change in frequency with respect to protein binding. It depicts that the oscillation frequency decreases with the increase in specific protein bindings on the sensor surface. Isansys has developed patient status engine (PSE), which is a wearable sensor patch that can continuously monitor a patient's vital signs and help predict the onset of sepsis in real time by analysing the physiological changes in the readings. Recently colorimetric detection of change in motion of multifunctional janus particle was used by Russell, Alba-Patiño, Borges, and de la Rica (2019) to detect procalcitonin (PCT) biomarker related to sepsis from whole blood.

A combined comparative summary of 5 sepsis sensing techniques realized using the last three approaches cussed above, detailing the samples they use, the biomarkers they target, the interfaces they utilize, their linearity and LOD, and their references, is presented in Table 6.

### 7 CONCLUDING REMARKS AND OUTLOOK

In this survey, we have provided a clear perspective on the current status of sepsis that is one of the most challenging medical disorders, with a discussion on its mechanism of action. In addition, a review of existing literature on sepsis diagnosis technologies and the areas wherein a fast and robust point-of-care sepsis detection system can be designed is also overviewed.

There has been a great advancement in the diagnosis of sepsis, especially in methods that do not require blood culture, such as PCR, MALDI-TOF and ELISA-based technology. These technologies have facilitated a great deal of velocity in which the infections along with their antimicrobial activity patterns are identified. However,

### Table 5 Survey on microfluidic and lab-on-chip sensors for sepsis diagnosis

| Principle          | Sample            | Biomarker | Interface | Linearity & LOD | Reference               |
|--------------------|-------------------|-----------|-----------|-----------------|-------------------------|
| Microfluidic       | Drop of blood     | Neutrophils | N/A       | N/A             | Ellett et al. (2018)    |
| Microfluidic       | Blood             | nCD64     | Cell counts | 619 ± 340 cells/chip | Zhang, Li, et al. (2018)|
| PoC microfluidic   | Blood             | nCD64     | Cell counts | 102 in 10 µl of Blood | Hassan et al. (2017) |
| biochip            | Buffer            | IL-3      | Magneto electrochemical sensing | 10 pg/ml | Min et al. (2018) |
challenges continue to persist and unless the clinicians can detect sepsis at its onset, the infected blood samples cannot be obtained from patients which results in retardation in diagnosis and delay in exercising antibiotics. Thus, there is an urgent need for point-of-care devices that can detect sepsis within minutes from the onset of sepsis. From the existing literature review narrated in this paper, it is evident that point-of-care biochips can be fabricated with the capability of detecting multiple sepsis biomarkers at a time. Thus, label-free biomarker detection can eventually pave the way for future automatic diagnosis of sepsis in intensive care units and thereby contribute significantly to the reduction in sepsis fatality worldwide.

In addition to the measurement issues, the occurrence of sepsis depends on a combination of system factors: hosts, pathogens and healthcare systems, as illustrated by the venn diagram in Figure 14.

![Figure 12](image-url)

**Figure 12** (a) Electrolyte-gated organic FET schematic and (b) implementation (Seshadri, Manoli, Marra, et al., 2018). Reprinted with permission from Elsevier. (c) Schematic of a nano-wire/aptamer FET-based label-free detection of IgE biosensor (Khung & Narducci, 2013)

### Table 6

Survey on FET, mass and machine learning-based sensors for sepsis diagnosis

| Principle                  | Sample      | Biomarker | Interface                                      | Linearity & LOD | Reference |
|----------------------------|-------------|-----------|------------------------------------------------|-----------------|-----------|
| Organic FET                | Saliva      | CRP       | Millimetre-sized transistor (SiMoT)            | 590 zM          | Macchia et al. (2019) |
| Colorimetry                | Whole blood | PCT       | Poly-3-janus transducers                       | 0.4 ng/ml       | Russell, Alba-Patiño, et al. (2019) |
| Machine learning based     | N/A         | N/A       | Prediction from variation of physiological data analysis of historic data available on sepsis | N/A             | Hu et al. (2018) and Khoshnevisan et al. (2018) |
| Electrolyte-gated OFET     | Buffer      | PCT       | Poly-3-hexylthiophene (P3HT)/antibody (anti-PCT) | 2.2 pM          | Seshadri, Manoli, Schneiderhan-Marra, et al. (2018) and Mulla et al. (2015) |
| Field effect transistor    | Buffer      | CRP       | CMOS Technology                                | 0.1 ng/ml       | Sohn and Kim (2008) and Park et al. (2010) |
| Quartz crystal microbalance—D300 QCM unit | Human serum | Folate-binding proteins | Au + Folate/ BSA + anti-FBP | 50 pM to 2 µM | nn |
These factors are interrelated and hence their interplay can be a crucial factor. The factors can be social and demographic which include diet, lifestyle, economic status, sex and race. Even access to healthcare system is very critical in determining the prevalence, extent and subsequent survival of a patient during the septic shock or severe sepsis. Also, clinical data are only available in high-income...
rate countries thereby limiting the correct statistical characterization of the diagnosis and its treatment results.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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