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Recent advances in biosensors for diagnosis and detection of sepsis: A comprehensive review

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ABSTRACT

Sepsis is one of the leading causes of mortality among critically ill patients globally. According to WHO report 2018, it is estimated to affect beyond 30 million people worldwide every year. It causes loss of human lives, which arise from infection and inflammation and long term stay in intensive care unit (ICU) in hospitals. Despite the availability of satisfactory prognostic markers contributing to the diagnosis of sepsis, millions of people die even after admission to the hospitals. Correct and early diagnosis of sepsis leads to rapid administration of appropriate antibiotics can thus potentially avert the attainment to critical stages of sepsis, thereby saving human lives. Conventional diagnostic practices are costly, time consuming and they lack adequate sensitivity and selectivity, provoking an urgent need for developing alternate sepsis diagnosis systems. Nevertheless, biosensors have the much-treasured scope for reasonable sepsis diagnosis. Advancement in nano-biotechnology has provided new paradigm for biosensor platforms with upgraded features. Here, we provide an overview of the recent advances in biosensors with a brief introduction to sepsis, followed by the conventional methods of diagnosis and bio-sensing. To conclude, a proactive role and an outlook on technologically advanced biosensor platforms are discoursed with possible biomedical applications.

1. Introduction to sepsis

Sepsis is an excessive or poorly regulated systemic inflammatory response that causes intravascular damage in the host (Gotts and Matthay, 2016). It remains an imperative cause of mortality in ICU patients, and therefore is a major concern for human health globally. In February 2016, during third international consensus, both the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) together revised the definitions of sepsis on the basis of clinical criteria. Revised definition stated that sepsis is a lethal organ dysfunction instigated by a dysregulated immune response to the infection (Singer et al., 2016). Although sepsis has long been recognized, it absolutely was not clinically outlined till the late twentieth century. Above all, result of the dearth of effective antimicrobials and supportive care prevented patients with sepsis from surviving long enough to be studied or to develop sequelae of organ dysfunction. An overview of pathophysiology of sepsis has been depicted in Fig. 1**a**. Multiple inflammatory pathways directly or indirectly get activated by the bacterial invasion and contribute to sepsis (Kanashiro et al., 2017). The primary mechanisms involved in these pathways are hyper activation of neutrophils, monocytes and macrophages followed by release of cytokines (Hack, 2000). Pathogenic components like lipopolysaccharide (LPS) interact with toll like receptors (TLRs) present over monocytes followed by induction of signaling cascade. Thereafter, transcription factor NF-kB activated contributing to the release of pro inflammatory cytokines such as TNF-α and IL-1 (Guolong Zhang and Ghosh, 2000). Considering the data of United States, the occurrence of severe sepsis has proportionally increased(approximately three hundred cases per one lakh population) (Rhee et al., 2017). According to annual national sepsis outcome report produced by the National Sepsis program, Ireland, the Irish sepsis-associated crude hospital mortality rate is 19%, the German mortality rate is 24.3% (Fleischmann et al., 2016b), and the Australian mortality rate is 17% (Kaukonen et al., 2014). In last decade, number of cases of sepsis has increased tremendously. It affects in large proportion to the patient admitted into the ICU of hospitals, where patients occupy over 2–3 lakhs bed per day with an average length of stay of 20 days and also contributing to 25% of fatalities in hospitals. A meta-analysis study reported that annual

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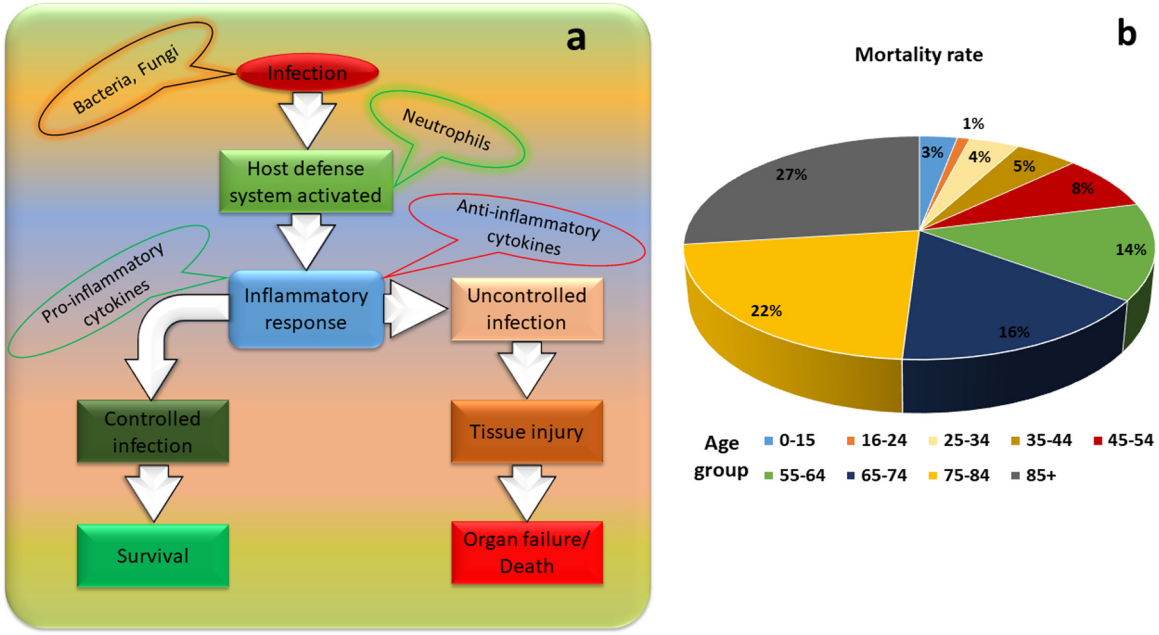

Fig. 1. (a) The schematic representation of sepsis pathophysiology; (b) Mortality rate based on age group.

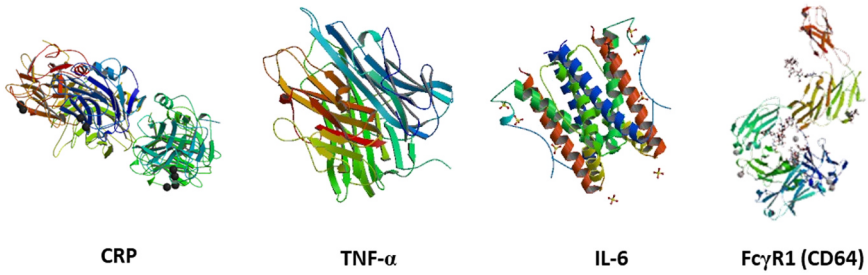

Fig. 2. Widely used biomarker for sepsis diagnosis (Images retrieved from the RCSB PDB (www.rcsb.org) of PDB ID 1BNA, 1A8M, 1ALU and 4W4O respectively from left to right).

incidence rates for sepsis is currently about 20.7 million globally and it is expected to increase gradually (Fleischmann et al., 2016a). Mortality rate based on the age has been depicted in pie chart Fig. 1**b**.

Although there are many preventive measures being practiced in hospitals worldwide, the overall sepsis mortality rate has been on the rise primarily due to infection caused by pathogens. Hence there is an utmost requirement to diagnose sepsis in early stages of its inception so as to prevent the severity of disease condition. Further, the mortality rate can be reduced effectively by providing proper medication at the right time. There are conventional methods being used for sepsis diagnosis primarily focusing onto the blood culture reports followed by molecular diagnostic techniques. However, conventional methods require multi-step analysis, hence time consuming, costly and need medically trained personnel for operation. Additionally, such methods are laboratory based, and the instrumentation used in such methods is not amenable to miniaturization. Hence, technologies that can overcome the disadvantages of conventional techniques needs to be developed and practiced clinically. Also, handheld point-of-care alternatives to the lab-based diagnosis should be developed so as to facilitate better healthcare. The best approach, moving forward, can be the implementation of highly sensitive biosensors for the diagnosis and detection of sepsis, providing helpful hand to the clinicians around the globe so as to control the alarming mortality rate. In the past few years, a large number of biosensors have been developed for the diagnosis of sepsis using different biomarkers, which can play a major role in sepsis pathophysiology. These biosensors yielded fruitful outcomes though interdisciplinary research-work, which further contributed to the advances in biosensors for diagnostic applications.

2. Markers for sepsis

Biomarkers are the biological molecule or features that acts as an indicator of physiological or pathological process. Monitoring the level of any biomarker in a specific biological media be it whole blood, plasma, serum, cellular fluid or any other, often proves critical in clinical diagnosis. Extensive research has been carried out towards identifying biomarkers for sepsis, understanding their impact, clinical significance, detection and quantification mechanisms. However, very few biomarkers have been translated in clinics for sepsis diagnosis. Some of the molecules which can be used as sepsis prognostic markers are shown in Fig. 2. In this section, we discuss these sepsis specific biomarkers in brief.

2.1. C-reactive protein (CRP)

CRP is primarily synthesized in the liver in response to factors released by macrophages. It is an acute phase protein whose level gets augmented after the infection and inflammation. Therefore, it is the most frequently used biomarker for both infection and inflammation diagnosis in clinical practice (Simon et al., 2004). It is believed that CRP may bind the phospholipid constituents of bacteria, thereby simplifying bacterial elimination by macrophages (Póvoa et al., 2005). The sensitivity and specificity of CRP as a marker for bacterial infections are 68–92% and 40–67%, respectively. Despite that, it remains useful for

sepsis prognosis and treatment progression. Increase in CRP levels can be correlated with degree of illness and severity of infection. Later on, the level of CRP starts declining could be due to clinical resolution of inflammation and response to antimicrobial therapy (Schmit and Vincent, 2008). The extensive accessibility of CRP makes it a convenient adjunct for diagnostic criteria. Conversely, CRP is not very much specific as compared to PCT which significantly restrict its percentage of specificity. It has been reported that CRP poses higher sensitivity to white blood cell count (Uzzan et al., 2006). Even though the clinical utility of such diagnostic approach remains uncertain.

2.2. Procalcitonin (PCT)

PCT is a precursor of hormone calcitonin, secreted by the C cells of the thyroid gland in human (Wacker et al., 2013). PCT has been studied extensively which enlightened the progressive response towards using it clinically (Suberviola et al., 2012). It has been unambiguously recognized that patients with sepsis have increased PCT level in their plasma and serum. It has also been reported that gradual decrease in PCT concentration has been observed between the second and third day of infection. Furthermore, it represents the increased survival rate in patient with infection (Jones et al., 2009). As it is known that pneumonia is the key infection contributing to sepsis, patients with community-acquired pneumonia are diagnosed positive and the level of PCT has been found to be high on first day. Thereafter, PCT decreases from day one to day three and further it is correlated with the mortality with 89% specificity, and 71% positive predictive value (Huang and Tang, 2015). This suggests that concentration of PCT is directly linked to the severity of illness in septic patients. In a clinical study, linear correlation was found between PCT and the severity scores of sepsis such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA scores) (Cardelli et al., 2008). Due to its specificity and resilient undesirable prognostic value, currently it is the most consistent biomarkers used in clinical practice.

2.3. Neutrophil surface receptor expression (CD64)

Fc-gamma receptor-1 (FcγR1), which is also known as CD64, belongs to the immunoglobulin family mostly expressed on macrophages and monocytes (Akinrinmade et al., 2017). In last few years, several studies have been carried out towards understanding the CD64 expression on neutrophil and were used to detect the presence of infection, that can cause sepsis (Looney, 1993). In healthy volunteer, CD64 was found to be expressed in very low quantity on neutrophil (Davis et al., 2006), while post-inflammation or infection, substantial elevation of CD64 expression on neutrophils were observed. Davis et al. (2006) reported a sensitivity of 88% and specificity of 77% for the presence of infection. CD64 expression onto the neutrophil were correlated with the presence of infection versus SIRS (Lewis et al., 2009), as well as the severity of sepsis (Hsu et al., 2011). Thus, CD64 can be used as prognostic marker for the identification of sepsis and can be directly correlated with the mortality in sepsis. CD64 has been proved to be a potential marker in diagnosis of sepsis (Livaditi et al., 2006).

2.4. Tumor necrosis factor-alpha (TNF-α)

Cytokines are the mediator of inflammatory response to infection. TNF-α,a pro-inflammatory cytokine, is amongst the widely studied pro-inflammatory cytokine in sepsis pathophysiology (Parameswaran and Patial, 2010). It contributes to activating endothelial cells with attracting neutrophils (Marie et al., 1996). Macrophage releases TNF-α within 30 min of infection, acting as mediator as well as regulator of innate immune response (Fiedler et al., 2006). It has been well reported that level of cytokine (TNF-α) in plasma gets elevated in sepsis patients (Kumar et al., 2018). Increased level of TNF-α causes worsening of inflammation with the assistance of other anti-inflammatory cytokines. Furthermore, it gets involved in organ damage leading to effective mortality of sepsis (Sun et al., 2015). Due to this mechanism it can become significant prognostic marker of sepsis which can predict it in early stage of such condition.

2.5. Interleukin-6 (IL-6)

IL-6 is a 21 kDa glycoprotein produced mostly by macrophages and lymphocytes. It is having potential effects in activation of B and T lymphocytes (Papanicolaou et al., 1998). It also has detrimental role in accumulation of lymphocyte and macrophage with the secretion of continuous Monocyte Chemoattractant Protein-1 (MCP-1) at the site of injury (Hack et al., 1989). IL-6 levels are found to be elevated in critical patient with infection and correlated with many indicators of disease severity (Borrelli et al., 1996). Clinical studies performed in patients after surgery with severe sepsis, have shown significant decrease in IL-6 within first week among survivors. Whereas, in non-survivors, IL-6 has been increased within the first week of infection (Tschaikowsky et al., 2011).

2.6. High-mobility group box 1 protein (HMGB-1)

HMGB-1 is a nuclear protein secreted by innate immune cells in response to infection and released by dying cells. It is found to be an abundant protein having role in pathogenesis of inflammatory diseases (Andersson and Tracey, 2011). There are manifold sources of HMGB-1, which is frequently released from monocytes (Sundén-Cullberg et al., 2005). It has effects in the activation of NF-κB, through the interaction of TLR-2 leading to activation of inflammatory cells (Lotze and Tracey, 2005). The HMGB-1 is promptly released subsequent to the infection. Also, it has been reported to have pro-inflammatory effects, and high plasma levels have been associated to sepsis. Further, it has been correlated directly to sepsis severity and organ dysfunction (Hatada et al., 2005).

3. Conventional methods for sepsis diagnosis

Sepsis diagnosis at early stages is very important and vital in terms of prevention as well as reduction in mortality. Conventionally, sepsis diagnosis is carried out by serological analysis and molecular techniques. The most important of these tests are discussed below.

3.1. Blood cultures (BC)

BC is used for pathogen detection in blood stream, and it has been termed as the “gold standard” in the diagnosis of sepsis. Despite this, it displays low sensitivity and is time consuming (24–72 h) (Mancini et al., 2015). It provides aetiology of infection in critically ill patients using their blood samples with an ultimate goal of antimicrobial therapy. Conversely, studies have reported that unsuitable antimicrobial therapy can be one of the risk factors contributing to the mortality in critically ill patients (Zaragoza et al., 2003). Considering prognostic views onto the positive blood culture results, it gives information that defense mechanism of patient has been compromised against infection (Riedel and Carroll, 2010).

Development of automated instruments, such as BACTEC™ FX/9000 series, BacT/ALERT series and VersaTREK have enabled improved and rapid detection of pathogens with enhanced sensitivity (Mancini et al., 2010a; O’Grady et al., 2008). In general, sensitivity of blood culture varies at different stages, starting from collecting the blood sample to loading of the sample on to automated BC instruments (Schwetz et al., 2007). It is to be noted, that the time-to-result in case of BC can also get delayed due to the slow growth of pathogens in broth. Thereafter, the performance of Gram stains has to be implemented afterward,it takes extra time for growth to yield single colony being used for the identification testing (Alvarez et al., 2012). Despite the advancements, for

patients with different types of infections, ratio of positive BCs to the number of patients differs significantly, which depends on the sepsis severity.

3.2. Molecular diagnostic techniques

Clinical laboratories nowadays progressively depend on molecular diagnostic techniques. Such techniques can perform diagnosis faster than BC, by reducing the time to pathogen identification and consenting for exposure of organisms missed by blood culture. These techniques are becoming more and more useful in contributing to the reduction of hospitalization and ICU stay, leading to a decrease in mortality (Caliendo et al., 2013). Several molecular methods have been technologically advanced for the identification of pathogens, whereas, polymerase chain reaction (PCR) has undoubtedly been the reliable choice due to its exquisite sensitivity and specificity. Other techniques include isothermal amplification methods, hybridization techniques and microarray techniques has been discussed below.

3.3. PCR-based methods

It allows the rapid detection of low numbers of pathogen by amplifying a specific target DNA sequence. PCR-based amplification strategies being used for sepsis detection has been discussed here in brief. Pathogen-specific assay is considered when the presence of a specific pathogen is suspected. This assay has been proven to detect *S. pneumoniae* in patients with infection, which is an evidence of pneumonia (Lorente et al., 2000; Mancini et al., 2009). Additionally, it is very useful in case of rapid diagnosis of invasive infections. Reportedly, it shows good sensitivity (79–100%) for the detection of aspergillosis or *candidaemia* (Kami et al., 2001; Wheeler et al., 2000). The assay has a limited use,due to the variation in pathogens, however, it can be used when specific infection is suspected. However, the clinical impact of the early detection remains to be proven. Broad range PCR assay has been established for the collective detection of both bacteria and fungi in blood. It is based on amplification of the signature gene of bacteria and fungi (Turenne et al., 2000). This approach is useful for negative blood cultures with the strong suspicion of bacteremia and fungemia (De Marco et al., 2007). Multiplex PCR assay involves amplifying multiple targets of DNA within a sample at a time, employing a mixture of primers designed to bind the targets to be amplified. It is highly favorable for routine practice for the diagnosis of bloodstream infections. The assay has characteristics to allow specific identification by means of limited pool of to some extent degenerated primers for PCR (Tsalik et al., 2010).

3.4. Mass spectrometry

A novel approach used for identification of bacteria has been reported, namely matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometry (TOF MS) (La Scola and Raoult, 2009). The MALDI-TOF system works by examining mass spectral signals obtained from post-culture samples based on the organism's proteomic profile, comparing to the standard reference spectra. It is additionally being used to identify bacterial virulence factors (Katussevani et al., 2002) and antibiotic resistance markers (Edwards-Jones et al., 2000). Most important advantages of this technique are the quick response time together with manpower being used very less compared to traditional methods. It is believed that the precision and dynamic range of this technique will advance in coming years as the quality of the information and methodology improves.

3.5. Hybridization

Furthermore, fluorescent in situ hybridization (FISH) has also been utilized in the detection of pathogens in blood cultures (Jansen et al., 2000). Briefly, in this method, blood culture slides are hybridized with oligonucleotide probes ($<$ 50 bp long) targeted to rRNA, and due to the fluorescent labels being used, it can be easily visualized in microscope (Oliveira et al., 2001). FISH is able to identify 95% of both bacteria and fungi present in blood (Marlowe et al., 2003). This assay allows the identification of numerous pathogens together within 60 min depending on the matrices used (Kempf et al., 2005).

3.6. Microarray

With the development of DNA microarrays, molecular technique enhanced in terms of specificity. Microchips has been coated with more number of bacterial targets to identify them all together in less time (Palka-Santini et al., 2007). One of the prototypes used for sepsis included six antibiotic resistance genes butwas able to detect limited pathogen such as *E. coli*, *S. aureus* and *P. aeruginosa* in positive BC (Cleven et al., 2006). In general, the clinical impression of microarrays can bequick, when a sufficiently broad panel of antibiotic resistance genetic markers are accessible and practiced straight to clinical samples.

Additionally, there aresome commercially available kitsfor the diagnosis of sepsis, and the same have been tabulated in Annexure 1 of the Supplementary material.

4. Sensors for sepsis and their classification

Biosensor is an analytical device that transduces biological reactions/events into quantifiable responses, like an electrical signal, which is proportional to analyte concentration. Elements of a typical biosensor has been shown into Fig. 3. Among different types of biosensors, electrochemical and optical sensors have been extensively used for sepsis diagnosis in the past. Additionally, magnetic sensors and immunosensors that rely on antibody-antigen binding have been greatly employed for sepsis diagnosis. Researchers have also explored miniaturized lab-on-a-chip platforms with integrated microfluidic channels for detecting sepsis specific biomarkers. Here, we briefly discuss some of the important contributions in this field.

4.1. Electrochemical sensors

An electrochemical sensor is a device that transforms electrochemical information into an analytical signal. In general, it consists of three electrodes (working, reference and counter) with an electrolyte, and it monitors the reaction kinetics at the electrode/electrolyte interface so as to provide the necessary transduction in terms of current, voltage or impedance (Bollella et al., 2017; Wan et al., 2013). Electrochemical biosensors have become popular over the years on account of their sensitivity, reproducibility and ease of fabrication & miniaturization. Surface modified working electrodes are widely used today for developing biosensors with high selectivity (Cho et al., 2018). Furthermore, electrochemical sensors have been integrated with microfluidic platforms for developing point-of-care devices for disease diagnosis. Herein, we discuss some of the electrochemical systems specifically developed for sepsis diagnosis.

In an attempt to detect the sepsis biomarker CRP, Miao and Bard (2003) covalently attached a synthetic single-stranded (ss) DNA (23-mer) on to an Au(111) substrate using a 3-mercaptopropanoic acid self-assembled thiol monolayer (SAMs). Using an anti-CRP-Ru-$(bpy)_3^{2+}$ modified Au working electrode, they showed a linear relation between the peak intensity and the analyte concentration over the range 1–24 μg/mL. In another work, Gupta et al. used a carbon-nanofiber based label-free biosensor (Gupta et al., 2014), wherein CRP detection in a wide range of concentrations (50 ng mL^{-1} to 5 μg mL^{-1}) with a limiting detection of 11 ng mL^{-1} was reported. Recently, a sensitive electrochemical sensor has been designed for the detection of PCT (Yang et al., 2017), where secondary anti-PCT-antibody was

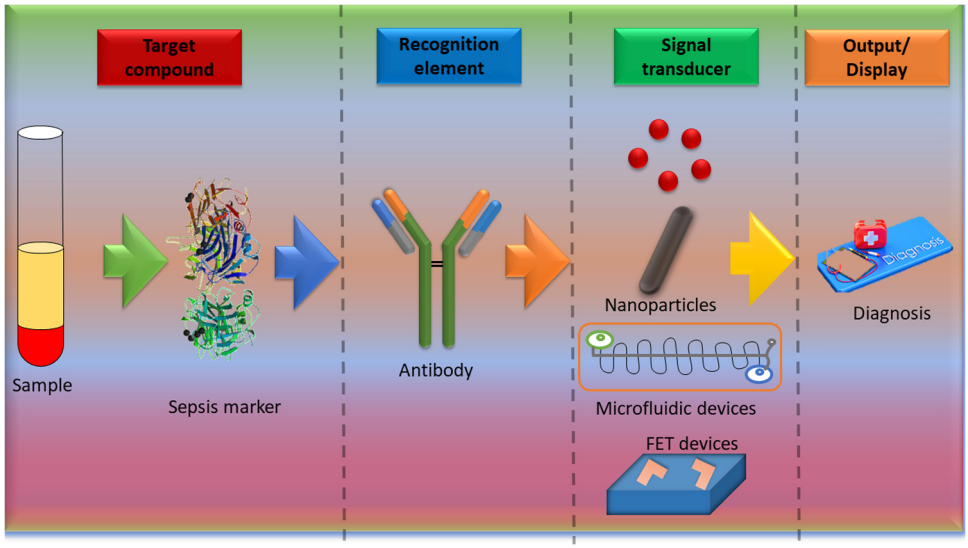

Fig. 3. Elements of Biosensor.

immobilized on to a CuMn-CeO_2 matrix. The sensor exhibited a linear range between 0.1 pg mL $^{-1}$ to 36 ng mL $^{-1}$ and the limit of detection was reported to be 0.03 pg mL $^{-1}$. Liu and Wang (2015) developed an electrochemical immunoassay using Au nanoparticles, where, the oxidization current varied linearly with PCT concentration, in the range 1.5 pg mL $^{-1}$ to 50 ng mL $^{-1}$, while the sensor displayed a limiting detection at 0.8 pg mL $^{-1}$. A platform for multiplexed and rapid pathogen identification in blood was reported by Gao et al. (2017), wherein, blood samples were prepared by spiking different bacterial species and the subsequent detection was done using a multiplex electrochemical sensor. For the reported work, the bacteria concentrations were in the range of 107–108 CFU/mL, and the limit of detection for *E. coli* was 290 CFU/mL. In another study aimed at sepsis detection, Lim et al. (2017) synthesized a series of synthetic peptides with cysteine residues at the C-terminus to facilitate thiol self-assembly. Therein, for PCT BP3 peptide, the authors reported a binding constant of 0.39 ± 0.11 nM for procalcitonin detection. Using monoclonal CRP-8 immobilized on to zinc oxide nanotubes, Ibupoto et al. (2012) realized a potentiometric platform for detecting CRP in human plasma. The system was used to detect CRP in the concentration range of 1.0 × 10–5 mg/L to 1.0 × 100 mg/L with the sensitivity being 13.17 ± 0.42 mV/decade. A functionalized double walled carbon nanotube modified dual screen-printed carbon electrode (SPCE) was used for simultaneous electrochemical detection of sepsis biomarkers, IL-1β and TNF-α, in human serum and saliva (Sánchez-Tirado et al., 2017). The authors implemented a sandwich type immunoassay wherein the immunosensor attributes to linearity in the range of 0.5–100 pg mL^{-1} and 1–200 pg mL^{-1} for IL-1β and TNF-α, respectively, wherein the ranges correspond to clinical relevance. Yang et al. (2013) reported an impedimetric immunosensor for the detection of IL-6, wherein, the sensor was synthesized by amperometric deposition of Au nanoparticles on to a horizontally aligned single walled carbon nanotube (SWCNT) array prepared in situ on a SiO_2/Si substrate. The sensor resulted in an LoD of 0.01 fg mL^{-1}, along with a wide linear response range (0.01–100 fg mL^{-1}). An amperometric biosensor based on enzyme conjugated acrylic microspheres and Au nanoparticles composite coated onto a carbon-paste SPE was fabricated by Nik Mansor et al. (2018). This enzymatic biosensor gave a linear range of 0.01–100 ng/mL with a detection limit of 5 × 10^{-3} ng/mL towards sPLA2-IIA. Eletxigerra et al. (2014) also reported an amperometric immunoassay for the determination of TNF-α in human serum, using magnetic microbeads and disposable SPCEs. Kongsuphol et al. (2014) addressed the issue of false positive detection on basis of the interference caused by serum background, and as an alternative to the said problem, they reported magnetic bead coupled electrochemical detection of TNF-α from non-diluted serum. Peng et al. (2011) synthesized silver nanoparticle–-hollow titanium phosphate sphere (AgNP–TiP) hybrid which was later used for labeled electrochemical detection of IL-6. The assay results in a detection limit of 0.1 pg mL^{-1} with a linear range of 0.0005–10 ng mL^{-1}. In a different work aimed at PCT detection, Li et al. (2015) described a new signal-amplification strategy utilizing a nanocomposite derived from amino-functionalized C_{60} nanoparticles, ferrocene carboxylic acid and platinum nanoparticles (PtNPs), which resulted in a detection limit of 6 pg mL^{-1}. Another electrochemical platform aimed at sensitive detection of TNF-α in undiluted serum was reported by Arya and Estrela (2017). A biosensor targeting impedance-spectroscopic detection of TNF-α was reported by Pui et al. (2013), wherein, the sensing platform also comprised of an SAM of dithiobis-succinimidyl propionate (DSP) on an Au electrode array. The performance of the Au-DSP-anti-TNF-α bioelectrode in presence of the TNF-α antigen was measured in the range of 1 pg mL $^{-1}$ to 10 ng mL $^{-1}$, and a detection limit of ~57 fM was reported. In yet another work aimed at the detection of TNF-α along with the detection of interferon (IFN)-γ, researchers utilized a micropatterned electrode array selectively functionalized with electroactive aptamers (Liu et al., 2012). The sensor resulted in a detection limit of 0.58 nM, with linear range extending up to 5.8 nM. For the multiplexed detection, neighboring electrodes were modified with separate set of aptamers, creating alternate sites for the capture of IFN-γ and TNF-α. Bryan et al. (2013) reported the development of a reusable impedimetric platform for label-free detection of CRP in blood serum, where the sensor accounted for a detection limit of 176 pM. Fabrication methods and other experimental details associated with the literature reported here are discussed in greater detail in Annexure 2 of the Supplementary material.

4.2. Optical biosensors

In addition to the electrochemical biosensors described above, a large number of optical sensors have also been developed in past for sepsis biomarker detection. Islam et al. (2010) reported a label-free quantification scheme for CRP based on molecular switching of fluorescence. In another work, Zamarreño et al. (2013) used an optical fiber device for CRP detection, wherein the device could effectively differentiate pathological concentrations of the target protein from non-pathological counterparts in fewer than 15 min. Rascher et al. (2014) reported a total internal reflection based point-of-care fluorescence

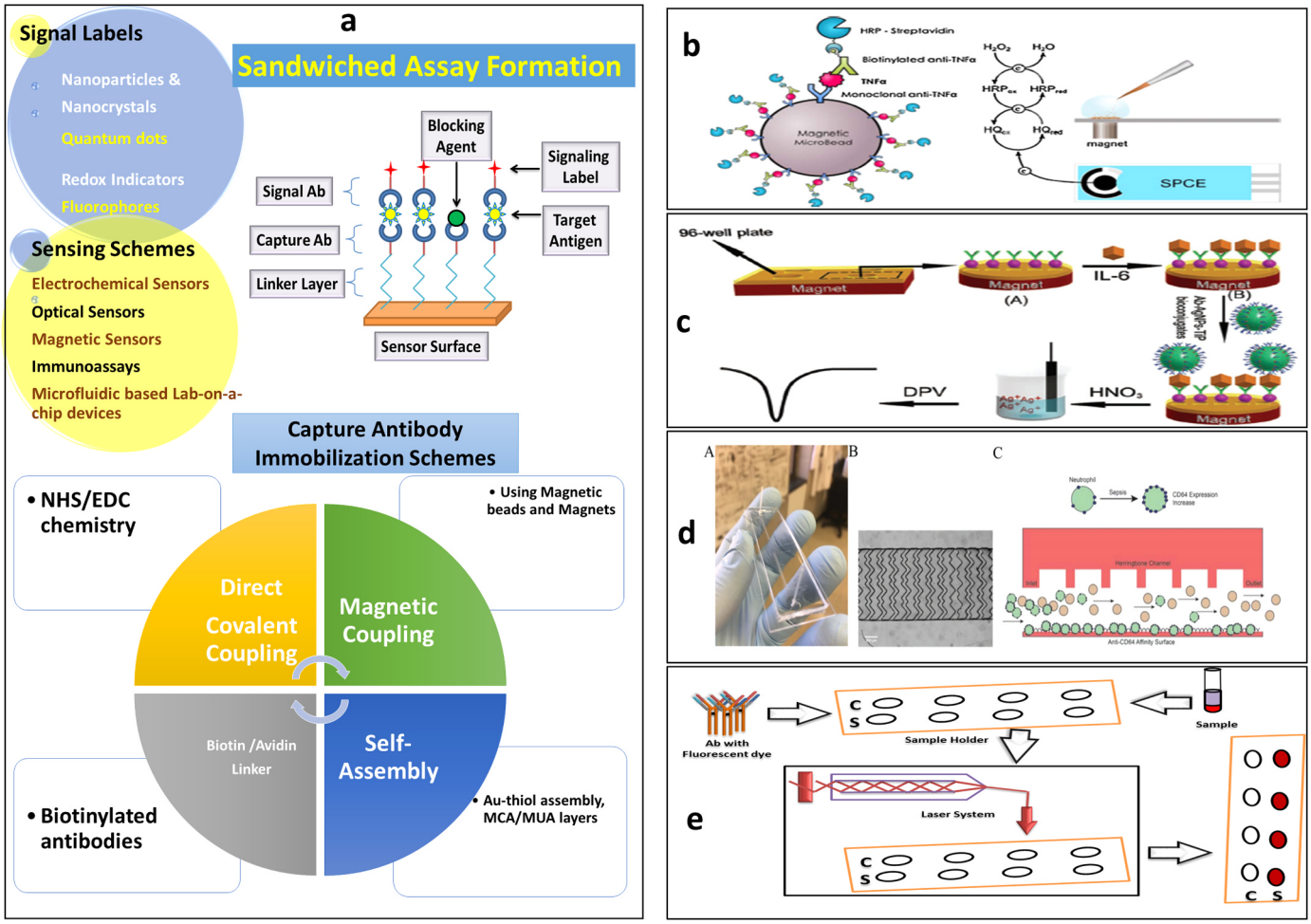

Fig. 4. (a) Schematic representation of a typical sandwiched assay showing different sensing schemes, signaling labels and antibody immobilization protocols; (b) Schematic display of the sandwich TNF-α magneto-immunoassay developed (Eletxigerra et al., 2014). "Reprinted with permission from (Eletxigerra et al., 2014). Copyright {2014} Analytica Chimica Acta." (c) Schematic illustration of electrochemical immunoassay of IL6. "Reprinted with permission from (Peng et al., 2011). Copyright {2011} Small." (d) Illustration of a Prototype of the Sepsis Chip containing cell capture channel for affinity separation using anti-CD64 antibodies (Y. Zhang et al., 2018). "Reprinted with permission from Y. Zhang et al. (2018) Copyright {2018} RCS." (e) schematic representation of fluorescence-based detection.

immunoassay for highly selective PCT detection. The assay, which utilized rat monoclonal anti-PCT-antibody, resulted in an LoD of 0.04 ng mL $^{-1}$ and a quantification limit of 0.12 ng mL $^{-1}$ in human plasma samples. Additionally, when applied to whole human blood samples, the assay resulted in an LoD of 0.02 ng mL $^{-1}$, with a limit of quantification amounting to 0.09 ng mL $^{-1}$. In a study, Fan et al. (2014) reported about a photoelectrochemical immunoassay using a co-synthesized TiO_2/CdS/CdSe complex, targeting IL-6 detection. An immunoluminometric detection scheme for PCT using a flash-type chemiluminescent immunoassay, that utilized isolated leukocyte subpopulations and acridinium-labeled anti-calcitonin monoclonal antibody, was reported by Tamas Koszegi (Köszegi, 2002). Kim et al. (2014) reported a nitrocellulose paper based optical biosensing platform for diagnosis of CRP in diluted serum, using a surface-sensitive refractive index measurement by a metal clad leaky waveguide (MCLW) sensor. Herein, the sensor chip was fabricated by depositing a 9 nm thick titanium layer followed by a 347 nm thick SiO_2 layer on to glass, on to which, a thin uniform nitrocellulose layer was spin coated. In another communication (Xiong et al., 2013), water-soluble high-quality $CuInS_2$/ZnS nanocrystals were used for developing a fluoro-immunoassay aimed at the IL-6 detection with a detection limit of 0.008 ng mL^{-1}. In another work targeted at localized IL-6 detection at significantly low concentrations in serum and culture media, K. Zhang et al., (2018); Y. Zhang et al., (2018) developed an optical fiber based sandwiched immunosensor that utilized biotinylated IL-6 capture antibody and fluorescent magnetic nanoparticle tagged detection antibody. The researchers report a detection limit of 0.1 pg mL^{-1}, with the linear detection corresponding to the concentration range of 0.4 pg mL^{-1} to 400 pg mL^{-1}. Jensen et al. (2005) developed a micro-structured polymer optical fiber using a PMMA rod for selective capture of α-streptavidin/α-CRP antibodies, leading to fluorescence-based analyte detection using Cy3-fluorophores. In a different work, targeting the detection of TNF-α, Petrovas et al. (1999) reported the development of an enzyme amplified lanthanide luminescence sandwich immunoassay, which used a capture antibody, a biotin-labeled monoclonal signal antibody, and an antibiotic-conjugated alkaline phosphatase. Using fluorimetric measurements, with 50 μL of sample volume consumption, the authors reported a detection limit of 1 ng/L, in a detection range extending up to 2000 ng/L. Kapoor and Wang (2009) used a combination-tapered-fiber-optic biosensor dip-probe to detect human IL-6 protein with a detection limit of 0.12 ng mL^{-1}. Targeting simultaneous detection of 15 human cytokines in stimulated peripheral blood mononuclear cells, Jager and team (Jager et al., 2003) developed a multiplex cytokine assay, which involved the use of carboxylated polystyrene microspheres for the antibody immobilization. A fluorescent nanospheres based lateral flow assay forCRP detection was developed by Hu et al. (2016), where the nanospheres comprised of 332 ± 8 CdSe/ZnS quantum dots (QDs). The authors reported a

detection limit of 27.8 pM, with a sensor stability of 6 months, an intra-assay variability of 5.3% and an inter-assay variability of 6.6%.

In addition to the above-mentioned research that targeted optical detection of sepsis biomarkers, a large number of surface plasmon resonance (SPR) based biosensors have also been developed in this direction. We feel, it is apt to discuss about some of the SPR based biosensing platforms targeting sepsis-detection in this section. Chammem and team (Chammem et al., 2014) reported about an SPR based platform for CRP detection in real samples, where towards the experimental setup for the SPR detection, a prism (refractive index of 1.7), a glass substrate with 16 gold spots, an excitation wavelength of 850 nm and a CCD camera was used. In another work aimed at SPR based detection of sepsis biomarker CRP, Yeom et al. (2013) used e-beam lithography to deposit Au layer on to which the capture anti-CRP antibodies were immobilized via an SAM. In their work, Meyer et al. (2006) talked about SPR based detection of CRP in blood serum, with a linear detection in the range of 2–5 μg/mL and a limiting detection of 1 μg/mL. Kitayama and Takeuchi (2014) also developed an SPR based platform for the detection of CRP in diluted human serum, by grafting poly (2-methacryloyloxyethyl phosphorylcholine) on to gold nanoparticles by surface-initiated atom transfer radical polymerization. Sener et al. (2013) developed a molecular imprinted polymer based SPR biosensor for the detection of PCT. As reported, the sensor accounted for a limiting detection of 9.9 ng mL^{-1} in both phosphate buffer and SBP, where the approximate detection time was less than 1 h. Another SPR based assay targeting the detection of PCT in real time samples was reported by Vashist and team (Vashist et al., 2016). As reported by the authors, the senor was capable of detecting PCT in the concentration range of 4–324 ng mL^{-1}, with the limit of detection and the limit of quantification being 4.2 ng mL^{-1} and 9.2 ng mL^{-1}, respectively. In another SPR based biosensor (Chou et al., 2010), detection of lipopolysaccharide induced IL-6 secretion from human fibroblast MRC5-CVI cells was targeted. In Annexure 3 of the Supplementary material, the above-mentioned optical biosensors are discussed in detail (Fig. 4).

4.3. Microfluidic based lab-on-chip devices and other integrated sensors

Microfluidic based lab-on-a-chip sensors are miniaturized devices that facilitate the integration of multiple functionalities of one/more sensing platforms on a single platform using low-volume samples. At the micro scale, such devices enable efficient detection of analytes at the expense of fairly low sample volume, reagents and energy (Lafleur et al., 2016), thereby paving the way for development of low cost, point-of-care devices. Currently, microfluidic lab-on-chip devices are being widely researched for potential applications in disease diagnosis. Here, we discuss some of the literature in regard to the detection of sepsis using microfluidic devices.

A microfluidic affinity separation device was developed to capture cells based on changes in CD64 expression in a single, simple microfluidic chip for sepsis detection (Hassan et al., 2017). In this work, an affinity capture method was developed to capture leukocytes based on changes in CD64 expression in a single microfluidic chip. In another study, a point-of-care microfluidic biochip was designed to enumerate leukocytes and quantify nCD64 levels (Rascher et al., 2014). A protein-microarray for simultaneous point-of-care quantification of sepsis associated serum proteins IL-6, IL-8, IL-10, TNF-α, S-100, PCT, E-Selectin, CRP and Neopterin was developed by Buchegger and team (Buchegger et al., 2012). Kim et al. (2017) devised a hybrid-biosensor system for the detection of PCT, CRP, and lactate. Colour signal produced from the assay was detected at a pre-determined time and quantified using a smartphone-based detector. Under the optimal conditions, the dynamic ranges for the analytes covered the respective clinical ranges, and the coefficient of variation was between 8.6% and 13.3%. In a different work aimed at rapid, point-of-care sepsis detection, Zhang et al. developed an integrated biosensor that analyses the pathophysiological role of IL-3 in early sepsis and employs a magneto-electrochemical sensor for its detection (K. Zhang et al., 2018; Y. Zhang et al., 2018). In (Schotter et al., 2009), authors have reported about a magnetic lab-on-a-chip prototype for point of care detection of sepsis biomarkers. Min et al. (2018) reported about an IBS (integrated biosensor for sepsis), whichprovides test-results within 1 h from native blood samples. The device detects IL-3 at a sensitivity of < 10 pg mL^{-1}; a performance which is > 5-times faster and > 10-times more sensitive than the current gold-standard. In Annexure 4 of the Supplementary material, the above-mentioned microfluidic platforms are discussed in detail. In the recent years, with advent of nanotechnology and advancements in nano & micro fabrication techniques, many advanced lab-on-chip devices are being fabricated that are leading us towards smarter healthcare. In a critical review (Buchegger et al., 2012), authors have summarized the recent innovations in optical microfluidic technologies for dedicated point-of-care diagnostics.

4.4. Immunosensors

Historically, immunosensors are analytical devices that use antibodies as recognition elements on account of their high affinity towards target molecules with a low dissociation constant in the nanomolar range. Immunosensors have found significant applications in fields ranging from disease diagnosis to food safety. Several types of antibodies (monoclonal, polyclonal and recombinant antibodies) are used in general to develop enzyme-linked immune sorbent assays and various other biosensor platforms. In immunosensing, antibodies are widely used as the capture probes on account of their sensitivity, ease of functionalization with nanoparticles and biomolecules, reproducibility and reliability.

Wang et al. (2006) developed an electrochemical immunosensor using poly-(guanine)-functionalized silica nanoparticles (NPs) for dual signal amplification based detection of mouse TNF-α. By virtue of a sandwich immunoassay method, guanine residues were attached on to the sensor surface using the poly(guanine)-functionalized silica nanoparticles, which were later catalytically oxidized in presence of Ru $(bpy)_3^{2+}$ thereby resulting in an anodic current. To form the sandwiched immunoassay, the authors incubated an anti-TNF-α modified SPE in desired concentration of TNF-α antigen, following which the electrodes were incubated in biotinylated-anti-TNF-α secondary antibody. In another work, Li et al. (2014) developed an electrochemiluminescent immunosensor with PCT-specific-nanobodies. In order to synthesize the nanobodies, the authors ligated synthetic human PCT cDNA into a pET32a vector and transformed the same into E. coli cells. Here, silica coated CdTe/SiO_2 quantum dot nanoparticles labeled with anti-PCT nanobodies were utilized as nano-immunological labels. The PCT specific capture nanobody was immobilized on to a chitosan–graphene nanocomposite modified glassy carbon electrode, which formed the target analyte binding surface. By virtue of a CdTe/SiO_2 nanoparticle-assisted ECL signal amplification, the sandwich assay resulted in a detection limit of 3.4 pg mL^{-1}. In an attempt to facilitate ultrasensitive detection of TNF-α, Yin et al. (2011) reported an alkaline phosphatase functionalized nanosphere based immunosensor, wherein, gold nanoparticle coated poly(styrene-acrylic acid) nanospheres were used to conjugate the alkaline phosphatase and the secondary anti-TNF-α antibody. The immunosensor used in this work was fabricated by electro-polymerization of a polyaniline/poly(acrylic acid) composite layer on a glassy carbon electrode, on to which, the primary anti-TNF-α antibody was covalently coupled. Presence of the target TNF-α antigen facilitated the formation of a sandwich assay between the immunoassay surface and the functionalized nanosphere, following which the labeled alkaline phosphatase catalyzed the formation of electroactive α-naphthol, which was amperometrically detected. The sandwiched immunoassay recorded a detection limit of 0.01 ng mL^{-1}, with electrochemical response being proportional to the logarithm of the target concentration in the range of 0.02–200 ng mL^{-1}. Rowe and coworkers reported a fluorescence based immunosensor for simultaneous

Table 1
Biosensors for sepsis detection.

Principle	Marker/ target	Components			Response / detection time	Linearity and limit of detection	Reference
		Recognition element	Transducer	Output			
Electrochemical sensors							
Optimised electrochemical biosensor	Blood serum	Anti-CRP	Gold electrode	Nyquist plots and EIS readings	–	LOD: 322 pM 176 pM	(Bryan et al., 2013)
Label-free electrochemical sensor	CRP	CRP specific antibody	Chip based electrode	Cyclic Voltammetry and EIS readings	–	LOD: 11 ng mL $^{-1}$	(Gupta et al., 2014)
Amperometric immunosensor	Pctab2	Antibody specific to PCT	Ferrocene-modified-Au-nanoparticles	Impedance and voltammetry response	–	LOD: 0.8 pg mL $^{-1}$	(Liu and Wang, 2015)
Electrochemical immunosensor	Pctab2	Antibody specific to PCT	Cu/Mn Double-Doped CeO_2 Nanocomposites	Impedance and voltammetry response	–	LOD: 0.03 pg mL $^{-1}$	(Yang et al., 2017)
Multiplex electrochemical sensor	Infected blood	Medium specific to bacterial species	AuNPs electrodeposited on SPE	Multichannel Potentiostat	–	290 CFU mL $^{-1}$	(Gao et al., 2017)
Electrochemical sensor	TNF-α	Anti-TNF-α	SAM	Impedance measurement		57 fM	(Kongsuphol et al., 2014)
Amperometric immunosensor	IL-1b, TNF-α	Antibody specific to IL-1b, TNF-α	Gold electrode	Amperometric signal	2 h 30 min	0.38 and 0.85 pg mL $^{-1}$	(Sánchez-Tirado et al., 2017)
Impedimetric immunosensor	Il-6	Antibody specific to il-6	Single-walled carbon nanotubes	Impedance response and voltammetry response		0.01 fg mL $^{-1}$	(Yang et al., 2013)
Amperometric immunosensor	TNF-α	Anti-TNF-α	Screen printed electrodes	Amperometric signal	60 min	5.8 pg mL $^{-1}$	(Eletxigerra et al., 2014)
Electrochemical immunosensor	Il-6	Anti-IL-6	Sphere conjugated with silver nanoparticle	Impedance response		0.1 pg mL $^{-1}$	(Peng et al., 2011)
Electrochemical immunosensor	TNF-α	Anti-TNF-α	Microaaray and ELISA	Differential pulse voltammetry		60 pg mL $^{-1}$	(Arya and Estrela, 2017)
Electrochemical aptasensor	TNF-α	Anti-TNF-α	Microfluidic channel	Square wave voltammetry		0.58 nM	(Liu et al., 2012)
Electrochemical immunosensor	PCT	Anti-PCT	Platinum nanoparticle	Differential pulse voltammetry		6 pg mL $^{-1}$	(Li et al., 2015)
Optical sensors							
Photo-electrochemical detector	IL-6	Anti-IL-6	TiO_2/CdS hybrid	spectral range of 200–2500 nm		0.38 pg mL $^{-1}$	(Fan et al., 2014)
Fluoro-immunoassay	IL-6	Anti-IL-6	$CuInS_2$/ZnS nanocrystals	Absorbance at 490 nm		0.008 ng mL^{-1}	(Xiong et al., 2013)
Fiber based immunosensor	IL-6	Anti-IL-6	fluorescent magnetic nanoparticle			0.1 pg mL^{-1}	(Y. Zhang et al., 2018; K. Zhang et al., 2018)
Optical immunoassay	IL-6	Anti-IL-6				0.12 ng mL^{-1}	(Kapoor and Wang, 2009)
lateral flow assay	CRP	Anti- CRP	nanospheres			27.8 pM	(Hu et al., 2016)
SPR sensor	CRP	Ab specific to CRP	gold surface	SPR response		10 pg mL^{-1}	(Chammem et al., 2014)
SPR sensor	CRP	anti-CRP	self-assembled monolayer	SPR response		100 ag mL $^{-1}$	(Yeom et al., 2013)
SPR sensor	CRP	anti-CRP	Using streptavidin-biotin chemistry	SPR response		1 μg mL $^{-1}$	(Meyer et al., 2006)
SPR sensor	PCT	Ab specific to PCT	KOH-treated gold-coated SPR chip	SPR response		4.2 ng mL^{-1}	(Vashist et al., 2016)
Lab on a chip and microfluidic devices							
Point-of-care microfluidic biochip	Blood	nCD64	PoC biochip	Cell counts		N = 102 in 10uL of patient's blood sample	(Hassan et al., 2017)
Microfluidic device	Blood	nCD64	Separation based on affinity	Cell counts		619 ± 340 cells per chip	(K. Zhang et al., 2018; Y. Zhang et al., 2018)
point-of-care testing device	PCT	monoclonal antibodies targeting PCT	TIRF-based quantification	assay to quantify PCT	9 min	0.04 ng mL^{-1}	(Rascher et al., 2014)
point-of-care platform	IL-3	HRP antibodies	magneto-electrochemical sensing strategy	assay to quantify IL-3	< 1 h	< 10 pg mL^{-1}	(Min et al., 2018)
Immunosensors							
Electrochemiluminescent immunosensor	PCT	Ab specific to PCT	chitosan–graphene nanocomposite	ECL signal		3.4 pg mL^{-1}	(Li et al., 2014)
Silica nanoparticle based immunosensor	TNF-α	anti- TNF-α	polyG functionalized silica nanoparticles	Using square wave voltammetry		60 aM	(Wang et al., 2006)

(*continued on next page*)

Table 1 (*continued*)

Principle	Marker/ target	Components		Output	Response / detection time	Linearity and limit of detection	Reference
		Recognition element	Transducer				
Nanosphere based immunosensor	TNF-α	anti- TNF-α	nanosphere	EIS signals		0.01 ng mL^{-1}	(Yin et al., 2011)
Fluorescence based immunosensor	Spiked blood	Enterotoxin B	array of biotinylated capture antibodies	CCD-based signal		50 ng mL^{-1}	(Rowe et al., 1999)
Miscellaneous							
Field effect transistor	CRP	anti-CRP	CMOS technology			0.1 ng mL^{-1}	(Kim et al., 2013)
Amperometric magneto-immunosensor	CRP	anti-CRP	magnetic disposable gold screen-printed electrode	amperometric measurements		0.021 ng mL^{-1}	(Esteban-Fernández De Ávila et al., 2013)

detection of several biomarkers along with D-dimer, a known biomarker of sepsis, in spiked clinical samples (Rowe et al., 1999). Vertically oriented PDMS flow channels were transferred on to neutravidin-coated planar waveguides, on which a patterned array of biotinylated capture antibodies was prepared. Post target antigen capture, a sandwich assay was prepared using labeled detector antibodies, which facilitated the fluorescence-based detection. Using a CCD-based optical readout, the authors were able to detect 50 ng/mL or higher concentrations of the sepsis biomarker D-dimer in buffer, plasma, and diluted whole blood.

4.5. Miscellaneous

In conjunction of the biosensing platforms described above under the four specific categories, several other sensing methods have also been reported in the literature aimed at sepsis monitoring. In a review article, Murkovic et al. (2003) reported about new sensing platforms for neonatal sepsis being incorporated in to the Neonatal Intensive Care Unit. They also provided a detailed overview of the emerging sensing technologies which are promising enough to be considered for routine neonatal monitoring practice in near future. In another elaborate review article, Al-Zahrani et al. (2015) presented a critical evaluation of the recent neonatal sepsis detection methods by comparing them with the more conventional counterparts. In a more specific study (Boo et al., 2008), a semi-quantitative procalcitonin test kit was reported for early diagnosis of neonatal sepsis. The authors conducted a real-time study by considering infants admitted to the neonatal intensive care units with signs indicative of a probable case of sepsis. As reported, the PCT quantification test kit resulted in an 88.9% prediction efficiency in detecting neonatal sepsis, with 65.2% specificity. In a study, Schulenburg et al. (2016) presented a Förster resonance energy transfer-based biosensor for the detection of neutrophil elastase. A target specific protein sensor that results in altered fluorescence upon selective cleavage by the target analyte at physiologically relevant concentrations was used in this study. As reported, on account of the proximity of the fluorescent proteins used in this study, the resonance energy transfer decreases upon the selective cleave induced by neutrophil elastase. In another communication, a point-of-care platform for real time human CRP detection in serum using a nano gap-embedded field effect transistor was reported (Kim et al., 2013). The sensor resulted in a limiting detection of 0.1 ng/mL, with a detection range of 0.1 ng/mL to 100 ng/mL. In another communication (Esteban-Fernández De Ávila et al., 2013), an amperometric magneto-immunosensor was developed and used for the detection and quantification of human CRP in serum. The method utilized a sandwiched assay based on covalent immobilization of a capture anti-CRP antibody onto –COOH group modified magnetic beads and a biotynilated secondary anti-CRP antibody. Using a magnetic disposable gold screen-printed electrode and amperometric measurements performed at − 0.10 V (vs. a Ag pseudo-reference electrode), in presence of tetramethylbenzidine and H_2O_2, the authors were able to achieve the desired CRP detection in the concentration range of 0.07–1000 ng mL^{-1} with reasonable linearity, along with a detection limit of (0.021 ± 0.005) ng mL^{-1}. Apart from these reported approaches, there are many molecular and non-culture-based methods for diagnosis of neonatal sepsis, which are critically reviewed by Mancini et al. (2010). Antiochia et al. (2015) in their review has discussed various affinity-based biosensors papers for the pathogenic bacteria detection whereas these bacteria somehow contribute to the sepsis.

We have summarized the biosensing platforms discussed above in a précised and categorical way below inTable 1. Furthermore, a discussion regarding the efficiency of these biosensors in terms of their analytical performance is presented in Annexure 5 of the Supplementary material.

4.5.1. Future perspectives and conclusions

It is critically vital to diagnose sepsis at early stages of its inception and advancement, which consents effective treatment sepsis patients, with high chances of recovery. Therefore, it is imperative to ensure development of simple and sensitive bio-sensing protocols that can detect multiple sepsis biomarkers at very low concentrations in biological fluids. Also, simultaneous detection of multiple biomarkers for better diagnosis is welcome. In the last decade, biomarker research on sepsis has taken a leap as it perceived many interesting molecules and functional entities. Among the biomarkers, CRP and PCT are the widely used markers clinically, whereas cytokines such as TNF- α and IL-6 and proteins such as HMGB-1 and CD-64 are used in molecular techniques.

Though conventional standard detecting approaches for sepsis are sensitive, they are inherently time taking, and hence cannot be completely dependable for diagnostic needs. Their slow pace makes them very much undesirable. On the other hand, advancements in the sepsis specific biosensor design due to the incorporation of nanomaterials, have significantly improved the sensitivity. Consequently, early and accurate detection of sepsis infection has been ensured, which was not the case with conventional techniques. Although more or less preliminary success has been accomplished in the field of sepsis diagnosis using target specific biosensors, but there is still a long run ahead. Electrochemical techniques are sufficiently sensitive and also a lot easier to practice but are pushed to corner because of lower selectivity and predominate use of labeled approaches. Reducing the overall complexity of the approaches, in terms of preparation and use protocols and data interpretation, is essential so as to develop point-of-care diagnosis tools. Also, cost effectiveness and shelf life of nanomaterial-based biosensors, that employ sandwiched assays with multiple antibodies and tagged nanoparticles, are matters of concern. The optical biosensors that utilize high-end instrumentation and sophisticated techniques for analyte detection also raise alarms in terms of their economic value and user-friendliness. For sensors that involve complex and costlier fabrication/synthesis protocols, reusability should be addressed and ensured, such that cost-per-diagnosis is maintained in an affordable range. In relation to the paper based and on-chip devices that are mostly for one time use and discard there are concerns in terms of their sensitivity. As an alternative, a sensing approach capable of simultaneously detecting multiple markers should be amended, as it would help in making correct clinical decisions with sepsis patients. With the incessant interdisciplinary determinations, owing to its miniaturization, time saving, low cost, portability, early diagnostics and numerous commercial applications will be making biosensors essential tools for sepsis management and diagnosis.

In this concern, most of the recent relevant articles were reviewed and the mechanisms of detection for different sensors were evaluated. Conclusively, it is expected that the biosensors developed using different types of nanomaterials will conquer a critical role in future applications for sepsis diagnosis.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bios.2018.10.034

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