Sepsis is a major cause of mortality among hospitalized patients worldwide. Rapid diagnosis is critical as early treatments have been demonstrated to improve survival. Despite the importance of early detection, current technologies and clinical methods are often insufficient due to their lack of the necessary speed, selectivity, or sensitivity. The development of rapid sensing platforms that target sepsis-related biomarkers could significantly improve the outcomes of patients. This Mini-Review focuses on the recent advances in rapid diagnosis of soluble biomarkers in blood with the emphasis on different configurations of point-of-care (POC) instruments. Specifically, it first describes the commonly targeted biomarkers and the mechanisms by which they are detected. Then, it highlights the recently developed sensors that aim to reduce the total time of diagnosis without sacrificing selectivity and limit of detection. These sensors are categorized based on their distinct sensing and transduction mechanisms. Finally, it concludes with a brief outlook over future developments of multiplexed sensors.

1. IMPORTANCE OF RAPID DETECTION OF SEPSIS

Sepsis is currently the number one cause of in-hospital deaths in the United States and the largest cause of death worldwide. Sepsis is a complex disorder that arises from a dysregulated immune response to an infection that leads to the extreme overproduction of cytokines. If left untreated, it eventually progresses to organ dysfunction, life-threateningly low blood pressure, and septic shock. However, early treatments can significantly reduce the mortality rate if administered in the early stages of sepsis before organ dysfunction. Thus, there is an urgent need for rapid and reliable diagnostic techniques to begin treatments promptly.

While clinical methods to identify sepsis exist, issues regarding their accuracy and analysis time remain. Guidelines such as the sequential organ failure assessment (SOFA), quick SOFA (qSOFA), and the systemic inflammatory response syndrome (SIRS) criteria evaluate patients for early and severe signs of sepsis based on common symptoms of organ failure. These symptoms include decreased blood pressure, elevated white blood cell counts, high respiratory rate, and altered mental status. These guidelines, however, have been criticized for their low predictive values and their inability to distinguish the cause for the deterioration of the patients’ conditions. Alternatively, testing of the patient’s blood sample (i.e., blood culture) can provide identification of the infecting pathogens and refine the appropriate choice of antibiotics treatment. However, the extended analysis time of such tests could cause a delay of treatment, where each hour delay is associated with an increase in mortality. Knowing the time scale of sepsis progression, it is relevant to delve into the development of a new methodology to complement current diagnostic techniques, with the goal of improving their speed and accuracy.

2. SEPTIC BIOMARKERS AND HOW TO DETECT THEM

As an alternative to the identification of the source of infection through blood culture, the detection of soluble biomarkers has the potential to have a much shorter analysis time. Sepsis induces the production of many biomarkers, and upward of 250 individual biomarkers have already been studied with varying success in clinical roles. While no single biomarker has been proven to be a specific indicator of sepsis, rapid detection of key biomarkers could provide useful diagnostic and prognostic values.

The current sets of biomarkers with the most predictive values are C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6). These biomarkers received the most attention in work focusing on sensor development and have been clinically linked to sepsis. CRP is synthesized in the liver and is one of the most common biomarkers of an infection or an inflammatory response. Accordingly, a blood concentration of CRP is highly elevated during the initial onset of sepsis, from below 3 μg mL⁻¹ for normal conditions to greater than 150 μg mL⁻¹. However, elevated CRP levels are not specific to sepsis
and could be affected by other conditions (e.g., autoimmune disorders, Crohn’s Disease, cancers, and obesity). Thus, its role as a prognostic biomarker overshadows its diagnostic values. That is, the decrease in CRP suggests the improvement of a patient’s health and effective treatment. PCT is a protein precursor to calcitonin and is produced within the thyroid. Its levels spike to greater than 2 ng mL$^{-1}$ upon the onset of sepsis and quickly dissipate to normal levels, approximately 0.15 ng mL$^{-1}$. Indeed, elevated levels of CRP and PCT are included in the clinical definition of sepsis. IL-6, a glycoprotein produced in macrophages, has been linked to the disease severity and higher mortality rate of sepsis. Typically present in concentrations below 15 pg mL$^{-1}$, its level rises to upward of 3 ng mL$^{-1}$ in a septic patient.

The biomarkers are commonly detected via recognition events with their respective antibodies functionalized on the biosensors. These antibody–antigen interactions are chosen due to their high level of specificity, potentially allowing the multiplexing of sensing components with minimal cross-reactivity. The recognition event is then transduced into quantifiable responses by various means depending on the type of sensors. We will focus on electrochemical and optical-based sensors as well as the methods of miniaturization using microfluidic platforms (Figure 1).

3. RAPID POINT-OF-CARE SENSORS FOR SEPTIC BIOMARKERS

This section of the Mini-Review identifies recently developed sensors targeting common septic biomarkers. Our purpose is not to provide an exhaustive list of sensors but rather to highlight key examples that emphasize speed, portability, and ease of use. For a complete historical overview of the field, we direct interested readers to comprehensive reviews by Kumar et al.$^{10}$ and Zhang et al.$^{11}$ We selected the following sensors, specifically based on their diagnostic speed (<1 h sample to results), ability to detect relevant concentrations of the targeted analytes, and the relatively small amount of sample required to produce accurate results. Additionally, these biosensors are highlighted as they make use of the most studied biomarkers and illustrate standard and multiplexed structures in a variety of fabrication methods.

3.1. Electrochemical Sensors. An electrochemical sensor transduces recognition events between a selector and an analyte into electrical signals. These signals include changes in current (amperometric), voltage (potentiometric), conductivity (conductometric), and impedance (impedimetric). They are typically fabricated with three electrodes: reference, counter, and working electrodes. The recognition units or selectors (e.g., antibodies) are immobilized onto the surface of the working electrode. Direct or label-free sensing is possible if the targeted recognition event produces changes in the electrical signal. Conversely, a secondary compound can be used as a label that mediates electrochemical events for indirect (labeled) sensing.

The key advantages of electrochemical biosensors include high sensitivity even at low concentrations, ease of fabrication, reproducibility, and fast analytical time. Furthermore, electrochemical biosensors have been shown to function at high levels of accuracy with whole blood samples and in multiplexed applications, reducing the sample preparation time. Early challenges involving low signal-to-noise ratios have been addressed using nanotechnology to shrink the physical dimensions of sensing elements and increase the number of recognition units. A common remaining issue involves fouling of the sensing interfaces, where an accumulation of undesired materials interferes with the signal.

Despite these concerns, electrochemical biosensors have been demonstrated as an effective means to reduce the time scale of biomarker detection. For example, Corrigan and co-workers developed an IL-6 sensor based around needle-shaped gold microelectrodes functionalized with a self-assembled monolayer (SAM) of IL-6 antibodies and potassium ferri-ferrocyanide as the redox agent (Figure 2a). The sensor demonstrated a clinically relevant limit of detection of 20 pg mL$^{-1}$ of IL-6 after 2.5 min of incubation in spiked human serum. Furthermore, Ingher and co-workers reported a multiplexed sensor targeting PCT, CRP, and pathogen-associated molecular patterns (PAMPs) in whole blood specimens without any cross-reactivity. The sensor comprised electrodes functionalized with a nanocomposite of cross-linked bovine serum albumin (BSA) and a network of reduced graphene oxide nanoparticles, to protect against biofouling and retain electrical connection. The selectivity arose from the use of antibodies for PCT, phosphorylcholine for CRP, and Fc-mannose-binding lectic for PAMPs. The oxidation and precipitation of 3,3′,5,5′-tetrathylbenzidine (TMB) were used to quantify the concentrations of the analytes. The authors highlighted that the analysis time could be reduced to under 10 min when coupled with a microfluidic device, and the reagent costs were only $0.08 per chip (and potentially less when manufactured at scale), which is promising for cost-effective integration with POC diagnostic tools.

Unlike the previous examples whose signals arise through the oxidation and reduction of the redox agents, Tanak et al. developed a sensor based on electrochemical impedance spectroscopy (EIS) that captures the binding interaction directly. The authors targeted PCT and CRP using respective antibodies immobilized onto thiolated zinc oxide electrodes. The semiconducting properties of zinc oxide were highlighted to...

Figure 1. Graphical representation of rapid sensing platforms for septic biomarkers covered in this Mini-Review.
increase the sensitivity of the sensor when the measurement was taken using nonfaradaic EIS, leading to results within 15 min and limits of detection in whole blood of 0.1 ng mL\(^{-1}\) and 0.1 \(\mu\)g mL\(^{-1}\) for PCT and CRP, respectively. Using a different device configuration, Torsi and co-workers demonstrated the use of an electrolyte-gated organic field-effect transistor (EGOFET) to detect PCT (Figure 2b).\(^\text{15}\) This sensor comprised a layer of poly(3-hexylthiophene) (P3HT) decorated with an anti-PCT antibody and bovine serum albumin (BSA). A characteristic transfer curve—drain current \((I_{DS})\) vs gate voltage \((V_{GS})\) at a constant drain voltage \((V_D)\)—shows the decrease in drain current with increasing concentration of PCT. Reproduced with permission from ref \text{15}. Copyright 2018, Elsevier.

The miniaturization of electrochemical sensors has led to several improvements, namely, the reduction of background currents associated with the electrode size, smaller resistive drop, and faster mass transport through the device. Collectively, these positive effects produce a larger signal-to-noise ratio. However, there are a few pressing issues associated with miniaturization. One is the potential increase in fabrication cost, which may become prohibitive for rapid and ubiquitous sensors. Moreover, devices with smaller dimensions may not be able to detect sufficient electronic transfer events to generate reliable signals. This issue has been resolved by many groups through signal amplifications and the engineering of novel electrode architectures (e.g., needle-shaped electrodes and nanogaps to facilitate rapid diffusion of analytes). Additionally, the incorporation of electrochemical sensors into microfluidic devices (Section 3.3) may produce rapid and practical POC instruments.

### 3.2. Optical and Fluorometric Sensors

Optical and fluorometric sensors often rely on antibody–antigen interactions similar to electrochemical sensors while transducing the signals using an optical mean. For example, a fluorescent dye can be attached to the recognition unit (e.g., sandwich assay structure) and detected through methods such as fluorescent microscopy. Optical sensors can provide high sensitivity and ease of multiplexing with different fluorescence-linked recognition units or colorimetric reactions. Similar to the miniaturization of electrochemical sensors, a principal concern for POC optical-based sensors arises from the need to produce a detectable level of signals. For example, spectroscopic methods can suffer from low resolution with low analyte volume.

Optical biosensors have been instrumental in the effort to reduce the time scale of sepsis diagnostics and represent the most common type of biosensors in the literature. For example, Zhang et al. developed a label-based sensor for IL-6 based on a sandwich assay structure on the surface of an optical fiber (Figure 3a).\(^\text{16}\) The label comprised a magnetic nanoparticle functionalized with FITC-avidin and IL-6 antibody. The author observed a linear relationship between IL-6 concentration in blood serum and a fluorescent signal with a limit of detection of 0.1 pg mL\(^{-1}\) and a working range of 0.4–400 pg mL\(^{-1}\). Most importantly, this sensor produced results after 1 min. Yin et al. reported a colorimetric sensor for IL-6 using antibody-functionalized gold particles and polystyrene particles with a secondary antibody and catalase.\(^\text{17}\) The two particles form a sandwich when exposed to IL-6 and subsequently catalyze the hydrolysis of hydrogen peroxide that regulates the deposition of silver ions onto the gold particles. As the concentration of IL-6 increases, the color signal (visible to the naked eye) changes from brown to yellow to light gray. The authors reported that the entire analysis can be completed within an hour with a limit of detection of 11 pg mL\(^{-1}\) of IL-6.

Though their design and operation are often more complex than their labeled counterparts, several groups have reported the use of label-free biomarkers for sepsis detection. Koukouvinos et al. developed a whole-blood sensor using white light reflectance spectroscopy (WLRS) that quantifies the concentrations of CRP based on the change in film thickness.\(^\text{18}\) Specifically, the antibody-functionalized surface was first exposed to diluted whole blood samples. The subsequent exposures to a biotinylated CRP antibody buffer solution and streptavidin solution increase the film thickness linearly with CRP concentrations. The whole process can be completed in 12 min with the limit of detection of 2.2 \(\mu\)g L\(^{-1}\) for diluted blood samples and 110 \(\mu\)g L\(^{-1}\) for whole blood samples. Wang et al. developed another CRP sensor using a surface plasmon resonance (SPR)-based methodology (Figure 3b).\(^\text{19}\) The authors used dopamine as a cross-linking agent to immobilize the CRP antibody onto the gold surface of an optical SPR sensor. By monitoring the peak shift of the reflected light (i.e., the change in refractive index) upon the exposure to CRP, the sensor observed a linear relationship within the range of 0.01 to 20 \(\mu\)g mL\(^{-1}\) and can achieve these results within 40 min.

### 3.3. Microfluidic Sensors and Micromotors

Microfluidic sensors are devices that combine microscale sensing operations and a controllable flow of analytes. As alluded in the previous
sections, microfluidic devices do not provide a unique transduction mechanism but often rely on the miniaturization of electrochemical and optical techniques. Indeed, they are a subclass of “lab-on-a-chip” devices whose structures are on the microscale. As a result, these devices are designed to be portable with reduced incubation time due to increased mixing of the sample solution. In many proof-of-concept devices, they are fabricated via soft lithography (e.g., with polydimethylsiloxane, PDMS) or photolithography, leading to the potential drawbacks of higher costs associated with microfabrication and operating equipment.

Valera et al. developed a microfluidic electrochemical sensor for IL-6 based on the sandwich array structure. This PDMS-based sensor included a capture chamber functionalized with IL-6 antibodies and relied on latex beads with a second antibody as the label. By measuring the variations in electrical impedance, the sensor achieved a limit of detection of 127 pg mL$^{-1}$ of IL-6 in blood plasma in 5 min. Using a similar methodology, Hassan et al. developed an electrical counting method to detect the number of leukocytes from 10 μL of whole blood to correlate with the onset of sepsis (Figure 4a). Specifically, PCT was first conjugated with a catalase enzyme using a competitive immunoassay and then captured onto magnetic beads functionalized with anti-PCT antibodies. Upon the exposure to hydrogen peroxide, the catalase enzyme generates bubbles that disperse the particles, leading to a detectable colorimetric signal. This sensor was able to achieve a clinically relevant limit of detection of approximately 1 ng mL$^{-1}$ in whole blood with only 13 min of analysis. This method of analysis holds great potential due to the ease of process automation, leading to a simpler transition to POC applications.

4. CONCLUSIONS AND OUTLOOK

The potential of sepsis diagnosis by biomarker sensing platforms holds many promises. The key advantages over conventional diagnostic methods include increased speed and efficiency of tests and smaller required analyte volume. Furthermore, the reduced reliance on PCR and blood culture tests may lower
operational costs and expand availability. Ultimately, the most important benefit is the potential for early diagnosis that leads to timely and successful treatment. These devices, however, are not without limitations. Similar to many sensing technologies, there are competitions between speed and accuracy. Mitigating false positives and negatives remains an important task. Issues associated with the miniaturization of the device arise from ensuring a detectable signal with sufficient signal-to-noise ratio at low concentrations. Additionally, the cost of implementing POC sensors should be rigorously evaluated. Currently, proof-of-concept devices are typically fabricated using lithography techniques that require access to clean room facilities. Moreover, the operations of such devices often require benchtop equipment (e.g., potentiostat, microscope, syringe pumps, and spectrometer), which may not be compatible with POC operations.

Despite the recent advances in rapid sensors, the diagnosis of sepsis based solely on the presence of protein biomarkers is currently not approved on a clinical scale by the United States Food and Drug Administration (FDA). Thus, the use of biomarkers serves only as a rapid confirmatory measure in conjunction with other standard methods. This is largely due to the difficulties in adhering to the FDA standards for Class II medical devices. Specifically, rigorous validation of the biomarker assays—including its precision, limit of detection, limit of quantification, linearity, specificity, and stability—must be demonstrated and quantified. However, there exist many examples of FDA-approved and commercially available sepsis sensors that focus on the detection of pathogens through PCR-based methodologies. As a result, many of these platforms operate on a time scale of several hours and require PCR or additional complex instrumentation, reducing their usefulness as a rapid POC tool.

Toward the development of a practical POC diagnostic tool for sepsis, another emphasis has been placed on multiplexing. Currently, most reported devices are optimized for a single analyte and may not provide sufficient diagnostic power. Despite the promising diagnostic and prognostic roles of biomarkers, no single marker is ideal or specific. Thus, an assay that could detect multiple key biomarkers and monitor their levels rapidly is critically important. Additional benefits of a multiplexed design could include faster analysis time and smaller sample volume. Furthermore, simultaneous detection of multiple septic biomarkers would offer the possibility of sepsis diagnosis at the earliest stages and provide a greater opportunity for physician intervention within the golden hour. Alongside the clinical validation, the development of reliable and rapid platforms for sepsis will contribute insights to early diagnosis and intervention that can reduce the mortality rate.

In conclusion, we presented a selection of recently developed biosensors for the detection of septic biomarkers with a focus on demonstrated speed and sensitivity. These metrics were chosen due to the importance of rapid detection of sepsis. The biosensors presented here were able to produce results within 1 h. Additionally, each sensor exhibited a limited detection below the clinically relevant concentrations of the targeted biomarkers. Furthermore, the performance of the biosensor was often tested alongside a currently used diagnostic method, showing comparable or, in some cases, increased sensitivity with a decreased time of analysis. It is our hope that this Mini-Review will serve as a short introduction to newcomers and developers in the area of biosensing platforms.

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Notes

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