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## Point of Care Technologies for Sepsis Diagnosis and Treatment

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### Abstract

Sepsis is a rapidly progressing, life threatening immune response triggered by infection that affects millions worldwide each year. Current clinical diagnosis relies on broad physiological parameters and time consuming lab-based cell culture. If proper treatment is not provided, cases of sepsis can drastically increase in severity over the course of a few hours. Development of new point of care tools for sepsis has the potential to improve diagnostic speed and accuracy, leading to prompt administration of appropriate therapeutics, thereby reducing healthcare costs and improving patient outcomes. In this review we examine developing and commercially available technologies to assess the feasibility of rapid, accurate sepsis diagnosis, with emphasis on point of care.

### Introduction

Sepsis is a life-threatening condition caused by the body's response to microbial infection, which triggers a cascade of events that can lead to organ failure and death.<sup>1</sup> Global estimates suggest that there were 31.5 million cases of sepsis in 2016, with 5.3 million resulting in death.<sup>2</sup> The Center for Disease Control reports that one in three fatalities in US hospitals are related to sepsis.<sup>3</sup> Neonatal sepsis is also a major concern, with the World Health Organization estimating an annual death incidence of over 1 million.<sup>4</sup>

The current standard for clinical sepsis diagnosis, referred to as Sequential Organ Failure Assessment (SOFA), was defined by the Third International Sepsis Consensus Task Force in 2016.<sup>5</sup> This scoring system informs of cumulative organ dysfunction that results from a dysregulated host response to infection. The SOFA score factors in respiration (arterial oxygen partial pressure to fractional inspired oxygen), coagulation (platelet count), liver function (bilirubin levels), cardiovascular function (mean arterial pressure or intervention), central nervous system function (Glasgow Coma Scale), and renal function (creatinine and

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Conflicts of Interest

There are no conflicts to declare.

urine output).<sup>5</sup> For each poorly functioning organ system, one point is assigned, with a score of 2 points or more representing a positive sepsis diagnosis. A positive SOFA score is associated with a hospital mortality rate of >10%.<sup>5</sup> Quick SOFA (qSOFA) offers a rapid alternative to SOFA by using only a subset of the SOFA scoring including altered mentation, systolic blood pressure below 100 mm Hg, and a respiratory rate of 22 per minute or greater.<sup>5</sup> qSOFA does not require laboratory testing and it can be repeated as needed. SOFA replaces the standard established in 2001 known as Systemic Inflammatory Response Syndrome (SIRS) criteria.<sup>6</sup> SIRS scoring involves two or more of: temperature greater than 38°C or less than 36°C, heart rate above 90 beats per minute, respiratory rate greater than 20 per minute, or white blood cell count greater than 12,000/μL or less than 4,000/μL.<sup>7</sup> SOFA has shown greater prognostic accuracy when compared to SIRS and qSOFA.<sup>8</sup>

Sepsis diagnosis has improved with the implementation of the SOFA scoring system; however, it still lacks specificity and requires multiple measurements. SOFA scoring leads to misdiagnoses in approximately 30% of patients, leading to unnecessary administration of antibiotics, which increases hospital costs and contributes to antibiotic resistance.<sup>9</sup> Given that survival rate decreases by 7.7% for every hour delay in the administration of antimicrobial therapy, rapid detection is vital for patient survival.<sup>10</sup> Additionally, many of the SOFA criteria require infrastructure and testing equipment, such as blood analyzers, that may be unavailable in developing healthcare communities. Due to these factors, it would be preferable to have a simpler, single test to diagnosis sepsis at the point of need that can replace SOFA scoring without decreased accuracy.

Point of care (POC) technologies based on biomolecular analysis provide rapid, actionable information to a patient or health professional at the time and site of evaluation and treatment.<sup>11</sup> These technologies are typically low cost, easy to use, and rapid with few infrastructure requirements making them applicable in a variety of settings worldwide.<sup>12</sup> Microfluidics,<sup>13</sup> lateral flow,<sup>14,15</sup> dipstick,<sup>15</sup> and smartphone<sup>16</sup> technologies have been used to investigate sepsis biomarkers such as proteins, nucleic acids, human cells, microbes, or pathogens.<sup>17</sup> POC technology is capable of utilizing small sample volumes, such as a fingerprick blood sample, and compact standalone devices or only the most basic laboratory equipment, such as microscopes. These factors allow POC diagnostics the potential to reach patients in limited-resource healthcare communities.<sup>12</sup> Additionally, use of POC testing at triage in US hospitals has been shown to reduce emergency room care times by 1 hour compared to traditional laboratory testing, decreasing hospital costs and saving lives.<sup>18</sup> POC diagnostics are actively being explored for nutrition,<sup>19–22</sup> infectious disease,<sup>11,13,23</sup> cancer,<sup>24–27</sup> and HIV/AIDS.<sup>28–30</sup>

Sepsis POC diagnostics are a potential solution for risk-stratification of new patients, guiding initial treatment, monitoring progression of infection, and evaluating patients' response to treatment (Figure 1A).<sup>31</sup> Ideal testing times should be on the order of tens of minutes to allow antibiotic intervention to prevent spread of infection and organ failure. POC tests used in US hospitals may require high diagnostic accuracy to compete with laboratory testing while low resource settings may prioritize inexpensive production, long-term low-cost storage, and ease of use.

Research on POC sepsis devices has been conducted using a variety of biomarkers (Figure 1B). Here we categorize them in three sections including blood plasma protein quantification, leukocyte monitoring, and pathogen detection. Relevant blood plasma proteins include C-reactive protein (CRP), procalcitonin (PCT), interleukins, and lactate. Leukocyte activity is measured through antibody capture or intrinsic property characterization while pathogen isolation is accomplished through many unique techniques such as magnetic separation. In this review, specific technologies are presented and evaluated for their respective advantages and disadvantages. Inclusion in this review is limited to the previous 10 years and application in a POC device or setting. A comprehensive review of all sepsis biomarkers outside of POC<sup>32–36</sup> and the pathophysiology of sepsis<sup>37,38</sup> can be found elsewhere.

## Assays for Blood Plasma Proteins

During sepsis, various proteins are expressed or secreted into the blood as a response to infection – cytokines, interleukins, acute-phase proteins, and receptor proteins concentrations are all increased. Presently, the most frequently investigated biomarkers for POC diagnostics are interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT).<sup>39</sup> IL-6 is a cytokine released near the onset of infection that correlates well with severity and outcomes in septic patients, where decreasing levels are predictive of survival.<sup>40,41</sup> A recent meta-analysis found the area under receiver operating characteristic curve (AUROC) value for IL-6 to be 0.79, indicating moderate diagnostic sensitivity.<sup>36</sup> CRP is expressed as a response to cytokines like IL-6<sup>42</sup> and has an AUROC value of 0.77.<sup>36</sup> PCT release is dependent on the severity of infection<sup>43</sup> with a half-life of around 24 hours and an AUROC value of 0.85<sup>36</sup>, where decreasing levels correlate with better survival rates.<sup>39</sup> IL-26 in combination with PCT exhibits greater diagnostic ability than either IL-26 or PCT alone.<sup>44</sup> Other proteins tested as standalone biomarkers include lactate, sTREM-1, neopterin, TNF- $\alpha$ , E-selectin, S-100, presepsin, LBP, CD64, DcR3, endocan, sICAM-1, and C3a.<sup>36</sup> Some of these markers have AUROC values greater than 0.9; however, the supporting literature is sparse so more extensive research is needed to be conclusive.

Single-analyte devices have the advantage of simplicity and are being tested for POC sepsis diagnosis. Blood lactate level has been used as a standalone sepsis biomarker for risk stratification of emergency room patients.<sup>45</sup> Gaieski *et al.*<sup>46</sup> reported that fingerprick sampling of lactate reduced the mean time from triage to result by 40% from standard laboratory analysis. Rascher *et al.*<sup>47</sup> have developed a microfluidic device to detect PCT via immunofluorescence with a limit of detection (LOD) of 0.04ng/mL in less than ten minutes. Okamura *et al.*<sup>48</sup> have developed an assay, called PATHFAST, to detect presepsin, showed higher specificity compared to other single biomarkers.<sup>49</sup> A chemiluminescent enzyme immunoassay is used to run whole blood samples with results in 17 minutes. Valera *et al.*<sup>50</sup> have adapted a previously designed biochip platform<sup>28,51,52</sup> to sense IL-6 using latex beads. Measurements with this device took 5 minutes each and the limit of detection was 127 pg/mL. Min *et al.*<sup>53</sup> are able to detect IL-3 levels within 1-hour using their POC device with a reported AUROC value of 0.91 (Figure 2). The smartphone functions as a touch-screen interface, as well as providing data storage and system controls. POC devices commonly

integrate smartphone technology due to their imaging, computation, communication, and networking capabilities, as well as their familiarity and simplicity to almost all age groups.<sup>54</sup>

Multiplexed biomarker detection has the potential to increase diagnostic power. Shapiro *et al.*<sup>55</sup> suggested the most effective panel to assess patient risk would include neutrophil gelatinase-associated lipocalin, interleukin-1ra, and Protein C. Buchegger *et al.*<sup>56</sup> have developed a miniaturized protein microarray chip for the detection of IL-6, IL-8, IL-10, TNF alpha, S-100, PCT, E-Selectin, CRP, and Neopterin. The device has been tailored for sepsis POC testing in neonates, building on a previous device.<sup>57</sup> Improvements include a reduced patient sample volume of 4 $\mu$ L, implementation of a single-step process, reduced incubation times, and the addition of internal calibration. For the previous iteration of this device, Sauer *et al.*<sup>57</sup> reported that the 2.5 hour single-step protocol suffered from lower sensitivity than the 4 hour multi-step protocol. However, the new device shows no loss of sensitivity when utilizing streptavidin conjugated magnetic particles to promote mixing and binding within the smaller sample volume. Complete sample processing was kept at 2.5 hours for the single-step process due to decreasing accuracy for analytes S-100 and CRP when incubation time was reduced. Kemmler *et al.*<sup>58</sup> have developed a microarray biochip using CRP, IL-6, PCT, and NPT. The device uses an on-chip immunofluorescence assay that lasts only 25 minutes and requires between 10–75 $\mu$ L of sample. However, due to the high LOD of IL-6 and PCT, this device is only applicable for clinically relevant levels in the mid to high range. The clinically relevant region of interest for PCT is between 0.05 and 50ng/mL, while the PCT LOD for this device is 0.34ng/mL. Schotter *et al.*<sup>59</sup> reported a magnetic lab-on-a-chip device for the detection of the sepsis-related cytokines IL-6, IL-8, IL-10, and TNF- $\alpha$  using embedded magneto resistive sensors.

## Leukocyte Intrinsic Properties as Immune Markers

Identifying and monitoring the systemic inflammatory response is important because immune-paralysis is common in late stage sepsis, so this can be used as a marker of sepsis imitiation and progression. Neutrophils have gained attention because of detectable changes in morphology, mechanics, and motility in septic conditions.<sup>1,59–62</sup> Neutrophil CD64 expression<sup>63,64</sup> has been shown to increase under septic conditions, making it a potential biomarker for sepsis.<sup>65–67</sup> In response to bacterial infection, neutrophil CD64 was demonstrated to be upregulated as early as 1 hour after infection.<sup>68</sup>

Zhang *et al.*<sup>69</sup> developed a POC device with a herringbone-shaped cell capture chamber for affinity separation of CD64 cells within 2 hours. The device demonstrated an AUROC of 0.90 when compared to sepsis diagnosis based on qSOFA in a trial of 10 patient samples.<sup>69</sup> The technology was then expanded to include CD69 and the combined panel increased the AUROC to 0.98 when tested with 12 qSOFA positive clinical samples.<sup>70</sup> Prieto *et al.*<sup>71</sup> used iso-dielectric separation to differentiate electrical properties of activated and non-activated leukocytes. Using mouse models, they demonstrated that their on-a-chip electrical cell profiling strongly correlated with flow cytometry.<sup>71</sup> This device offers continuous monitoring of sepsis progression; however, it has not been tested clinically. Hassan *et al.*<sup>72</sup> designed a microfluidic biochip to electrically quantify CD64 antigen expression on neutrophils (Figure 3A). Their device can produce test results in 30 minutes and offers an

alternative to hematology analyzers and flow cytometers which may not be available in a POC setting.<sup>72</sup> This technology builds on previous POC devices that electronically quantifies cells from whole blood samples.<sup>52,73,74</sup> This device demonstrated an AUROC of 0.77 which is better than the AUROC of a subset of SIRS parameters (temperature, pulse, respirations and systolic blood pressure) which was found to be 0.7.<sup>72</sup> Applications of cell capture and quantification on a chip is not limited to sepsis, and reviews of these technologies can be found elsewhere.<sup>75–77</sup>

Neutrophils undergo changes in their intrinsic properties during infection and observing them can inform on disease progression. The most frequently studied is neutrophil motility.<sup>9,60,61</sup> Neutrophils, even once isolated from blood, exhibit a spontaneous migration signature specific to sepsis.<sup>61</sup> Ellet *et al.*<sup>9</sup> created a microfluidic assay to capitalize on this principle (Figure 3B). Using continuous fluorescent imaging and a machine learning algorithm, they quantified reverse migration, oscillation, and pauses of neutrophils isolated from a finger prick blood sample. The assay is robust, requires minimal handling, and automated imaging and analysis. It requires a four-hour time-lapse microscopy step followed by two-and-a-half-hour image processing, a longer time scale than some POC technologies but still clinically relevant. In a double blinded clinical trial using SOFA scoring, the device obtained an AUROC of 0.99 with 97% sensitivity and 98% specificity.<sup>9</sup>

While many of the blood plasma assays and leukocyte technologies hold promise, there is not currently a point of care technology that has sensitivity and specificity in the 90<sup>th</sup> percentile and can produce results in under an hour.

## Pathogen Isolation as a Diagnostic and Treatment

With advances in miniaturization and development of lab-on-a-chip systems, direct isolation and detection of pathogenic bacteria from the blood for sepsis therapy and diagnosis has been explored. Microfluidic devices for pathogen isolation, lysis, and DNA extraction have been reported to identify pathogens and aid in antibiotic selection. Techniques utilizing dielectrophoresis, inertial effects, surface acoustic waves, and centrifugal microfluidics have been developed for separation of infectious agents from blood cells. Lab-on-a-chip systems with integrated bacterial separation, chemical or mechanical cell lysis, and DNA extraction for PCR or sequence specific capture have shown promise for rapid sepsis diagnosis.<sup>78–80</sup>

Artificial spleen type devices for the direct removal of pathogens and endotoxins from whole blood were developed for therapeutic applications (Figure 4A). Similar to dialysis, these devices process whole blood by capturing a broad range of infectious agents using ligand and antibody coated magnetic beads,<sup>81–85</sup> porous membranes,<sup>86</sup> biomimetic cell margination,<sup>87,88</sup> acoustophoresis,<sup>89,90</sup> and elasto-inertial-based migration.<sup>91</sup> Table 1 lists the miniaturized pathogen removal devices for sepsis treatment. A comparison of pathogen separation rate and removal efficiency is shown among these devices. Lee *et al.*<sup>84</sup> developed magnetic nanoparticles modified with a synthetic ligand that binds to both Gram-positive and Gram-negative bacteria. Yung *et al.*<sup>82</sup> developed mannose-binding lectin (MBL) coated magnetic nanobeads that do not activate complement factors or coagulation (Figure 4B,C). They reported processing of up to 1.25 L/hr of blood and greater than 90% removal of

pathogenic organisms in rats. Lopes *et al.*<sup>85</sup> reported separation of six Gram-positive species, two Gram-negative species, Methicillin-susceptible *Staphylococcus aureus* (MSSA), and Methicillin-resistant *Staphylococcus aureus* (MRSA) in whole blood via mutated lysozyme coated magnetic beads. Hou *et al.*<sup>87</sup> developed an extracorporeal biomimetic microfluidic device based on microcirculatory cell margination for non-specific removal of pathogens and cellular components. This method can reach up to ~1–2 L/hr throughput and when multiplexed could produce a 100-fold higher throughput. An acoustic microfluidic method (Figure 4D, E) was recently reported by Ohlsson *et al.*<sup>89,90</sup> based on size separation of pathogens. This method is label-free and resulted in a greater than 80% bacterial separation from a whole blood sample. These miniaturized devices for sepsis pathogen removal have a potential for POC applications. By improving clearance rates and efficiency, these devices could be effective in aiding sepsis treatment. Separation rates similar to blood dialysis machines (~ 1–2 L/hr) would require at least 5 hours to filter all the blood from an average person. Since survival decreases by the hour, a flow rate closer to ~4–5 L/hr is more desirable for therapeutic POC applications. Such characteristics can be achieved by 1) multiplexing microfluidic devices for high throughput, 2) utilizing high affinity target binding antibodies, and 3) minimizing technological complexity for separation.

The blood cleansing approach is promising for the direct removal of pathogens from blood, however, this method will not remove infection localized within organs. With the blood cleansing technology in infancy, significant processing times of several hours are required to remove the circulating infection which is slower than desirable. The removal of blood pathogens has been shown to delay disease progression, providing time to identify the contamination and administer targeted antibiotics, thus improving overall survival. Combining on-chip DNA extraction and blood cleansing technology could be used to perform pathogen-specific analysis while targeted antibacterial therapies are investigated.

## Commercial Devices

Most of the technologies discussed thus far are in research and development, but it is also important to consider those that are commercially available. Commercial technologies currently available for sepsis diagnosis range from simple devices like blood analysers to more complex systems for molecular diagnostics and mass spectroscopy. Table 2 provides a complete summary of commercially available diagnostic technologies for sepsis, with an evaluation of their feasibility at the POC. We have categorized them into blood analysers, microbiology based, molecular diagnostic based, and pathogen removal. Currently, most of these methods require microarrays, polymerase chain reaction (PCR), or other complex laboratory equipment that may be unavailable in low resource settings. We predict that the commercial market will also experience a shift towards POC sepsis diagnostics in the coming years.

Bacterial cultures are time consuming (24 to 48 hours), delaying the switch from broad spectrum antibiotics to more effective targeted therapies. Mature molecular diagnostic techniques such as PCR and fluorescent in-situ hybridization (FISH) have emerged as rapid diagnostic alternatives for pathogen identification.<sup>92–94</sup> These techniques require up to 12 hours, but recently, turnaround times as small as 30 minutes are reported for the



identification of 14 bacterial species by a Miacom system using FISH from positive blood culture test. Standard blood culture takes 1–3 days to increase bacterial concentration to the detectable limit for molecular diagnostic testing. By eliminating the blood culture, technologies such as Septifast (Roche) can identify 25 different common sepsis pathogens within 6 hours, DiagCORE (STAT Diagnostics) can perform a 48 plex real-time PCR test that recognizes relevant pathogens in 30 to 80 minutes, and T2 *Candida* panel detects fungal infections in whole blood samples using a PCR system. Although commercial systems exist, many of these technologies are not suitable for POC use. The research on sepsis POC technologies highlighted in this article could reduce the time to detection and aid in targeted antibacterial therapies at the point of need.

Commercial biomarker tests that indicate early organ dysfunction and predict septic shock have been developed. Molecular fingerprinting prior to and during treatment, including cytokine profiling<sup>95–97</sup> and PCT tests,<sup>98</sup> are being clinically evaluated. Many innovations are unfolding in the biomarker space such as adrenomedullin, which is a biomarker for septic shock shown to increase in blood 1–2 days before shock occurs.<sup>99</sup> Devices for extracorporeal filtering of the infection also exist in the market. Products like Cytosorb (CE-marked) filter proinflammatory cytokines to control immune response while Alteco Medical's LPS Adsorber and Spectral Medical's LPS-binding Toraymyxin devices remove endotoxins released by pathogens. For POC applications, there is a need to develop and improve these commercial devices for both rapid and accurate diagnosis of sepsis.

## Conclusions

In this review, we examined developing and commercially available technologies to assess the feasibility of rapid, accurate sepsis diagnosis with emphasis on POC. As with many technologies, there is conflict between speed and accuracy. Some of these devices, such as the EPOC Blood Analysis System (Siemens Healthineers), are very fast but have limited use and require secondary testing and evaluation for a complete diagnosis. Others have strong monitoring potential but take hours of complex analysis.

Studies indicate that diagnosing sepsis using a single biomarker is challenging,<sup>100</sup> however, biomarker panels have shown promise.<sup>56–58,101</sup> Additional barriers to pathogen detection exist due to the breadth of infectious agents, relatively high limits of detection, and long culture times. Recent research has produced strong evidence for the use of immune system markers as indicators of sepsis over serum biomarkers. Neutrophils have been of special interest due to their critical role in innate immunity and rapid response to infection.<sup>102</sup> We predict that markers of the immune response to sepsis will continue to be well studied in the coming years.

Some experts have called into question the homogeneity of sepsis as a disease.<sup>103–109</sup> They argue that the term sepsis itself is too broad and that different classifications of sepsis should exist. If this is true, a single diagnostic device for all types of sepsis may not be possible. Based on a functional analysis, Sweeny *et al.*<sup>103</sup> proposed three subtypes of sepsis: inflammopathic, adaptive, and coagulopathic. Davenport *et al.*<sup>107</sup> suggest two phenotypes based on immune response states, prognoses, and genetic variation, whereas, Wong *et al.*

<sup>104–106</sup> proposed three subtypes based on genome-wide expression profiling. The heterogeneous disease progressions and immune responses associated with sepsis, may be unminding the efforts to standardize diagnostics and treatments. Additional research is required to determine the extent of heterogeneity in sepsis and the corresponding effects on diagnostics and therapies. It is possible that, rather than a single biomarker or panel to diagnosis all cases of sepsis, it will be necessary to utilize different diagnostics at different times and for different subsets of septic patients.<sup>100</sup> We predict that research on the homogeneity of sepsis will be of increasing interest in the coming years.

The transition to SOFA scoring makes benchmarking POC diagnostic devices challenging. While some devices are tested against SOFA scoring, others are still being tested against less accurate SIRS scoring.<sup>5,8,9,110</sup> A standardized protocol for comparison should be established to increase the power of reported results. POC devices should continue to be designed with an emphasis on low-cost and long term stability, and additional thought should be given to how diagnostic outcomes can inform treatment. Additionally, further development of diagnostics could expand the ability to differentiate stages and progression of sepsis, rather than septic versus not septic.<sup>100</sup> POC technology for the diagnosis or treatment of sepsis would be especially beneficial due to the rapid disease progression and impact on populations worldwide. A successful POC sepsis diagnostic could improve health care access, save lives, reduce healthcare costs, and minimize suffering both in countries with well-developed healthcare systems and in low-resource settings. In the last 10 years, significant progress has been made, but additional research is vital to develop a successful POC device for sepsis.

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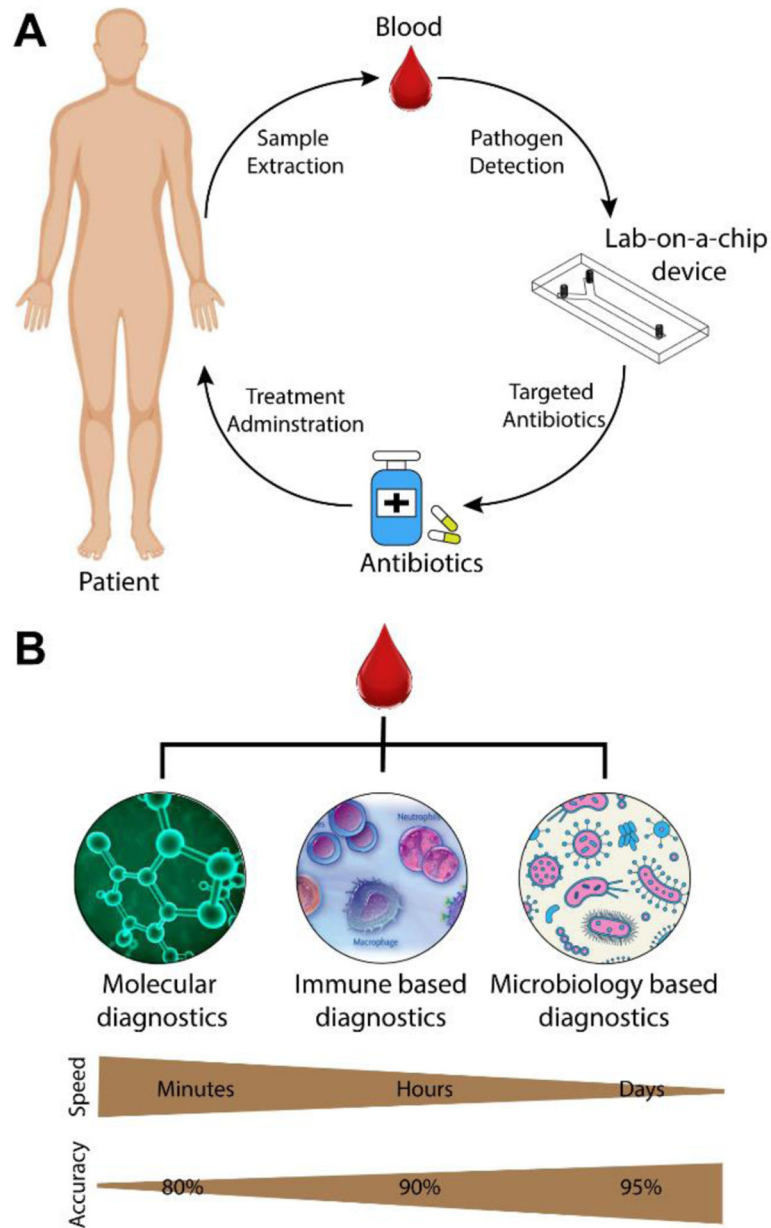


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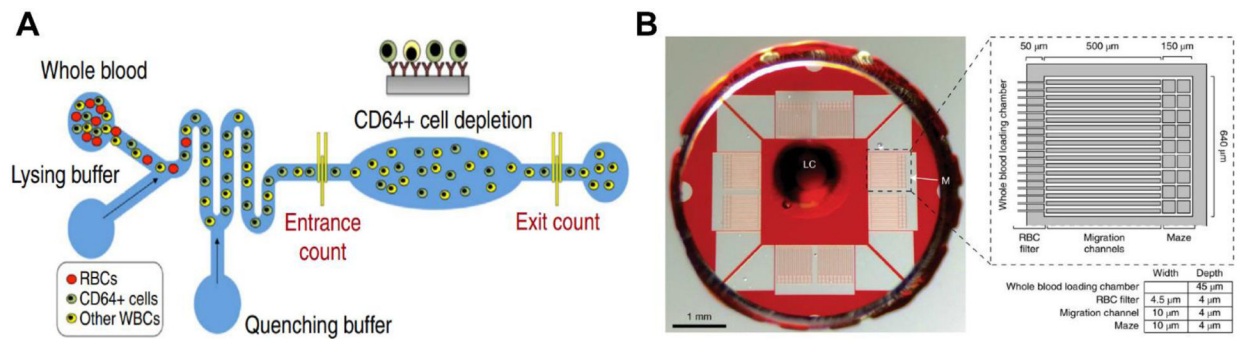
**Figure 1.**

A) Recommended use of POC sepsis chip in clinical care. Adapted with permission from Ref. 69. B) Categories of whole blood sepsis diagnostics are listed on the top and ordered by relative speed and accuracy depicted as gradients on the bottom.



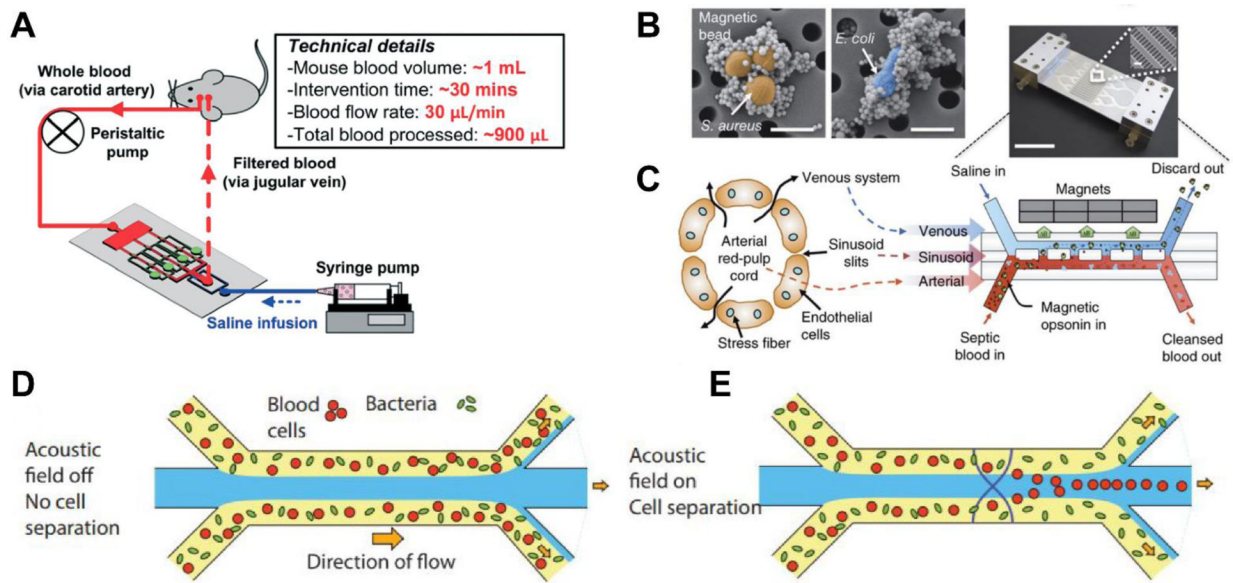
**Figure 2.** Example smart phone enabled POC interleukin detection device. Reproduced with permission from Ref. 53.





**Figure 3.**

A) Microfluidic CD64 expression quantification device with lysing and quenching zones for erythrocyte removal. False-colored fluorescent image of CD64+ cells captured on anti-CD64 coated pillars in the CD64 cell depletion zone. Reproduced with permission from Ref. 74. B) Microfluidic assay for spontaneous neutrophil motility from a drop of blood. Reproduced with permission from Ref. 9.



**Figure 4.**

A) Example pathogen removal apparatus. Adapted with permission from Ref. 86. B) Magnetic bead capture of *S. aureus* and *E. coli*. Reproduced with permission from Ref. 81. C) Magnetic opsonin and biospleen device for pathogen removal and blood cleansing. Reproduced with permission from Ref. 81. D-E) Acoustic separation of bacteria and blood cells. Reproduced with permission from Ref. 89.

**Table 1.**

State-of-the-art pathogen removal devices and techniques

Group	Device	Targets	Separation method	Sample	Separation Rate	Reported Pathogen Clearance
Ingber <sup>80</sup>	Microfluidic	Fungi ( <i>C. albicans</i> )	Magnetic separation with antibody coated beads	Whole blood	20 ml/hr	80%
Kohane <sup>84</sup>	Microfluidic	<i>E. coli</i>	MNPs modified with bis-Zn-DPA	Bovine whole blood	60 ml/hr	100%
Ingber <sup>81</sup>	Microfluidic	<i>S. aureus</i> , <i>E. coli</i>	Magnetic beads with engineered human opsonin-MBL	Rat whole blood	1.25 L/hr	>90%
Russom <sup>91</sup>	Microfluidic	<i>E. coli</i>	Elasto-inertial microfluidics with viscoelastic effect	Whole blood	60 µl/hr	76%
Han <sup>87</sup>	Microfluidic	<i>E. coli</i> , leukocytes, cytokines	Passive cell migration	Spiked whole blood	150 ml/hr	70%
Kreiger <sup>85</sup>	Manual	Six Gram-positive and two Gram-negative species, MSSA, MRSA	LysE35A-coated beads	Whole blood	N/A	85%
Zhan <sup>86</sup>	Microfluidic	<i>E. coli</i>	Porous polycarbonate (PCTE) membrane with 2 µm pores	Whole blood	50 µl/min	22%
Laurell <sup>90</sup>	Microfluidic device with acoustic transducer	<i>P. putida</i>	Size based separation using acoustic impedance	Whole blood	200 µl/min	80%

Table 2.

## Commercially Available Technologies for Sepsis Diagnosis and Treatment

Device	Company	Technology	Sample	Turnaround time	Sepsis Diagnosis	FDA clearance	Point-of-care?
<b>EPOC® Blood Analysis System</b>	Siemens Healthineers	Blood gas analyzer with room temperature test card	Whole blood	< 1 min	qSOFA scoring	Yes	Portable, 92 ul blood sample
<b>Septi-Chek</b>	Becton Dickinson	Blood culture with media	Whole blood	~38 hr	Pathogen identification	Yes	Requires laboratory equipment
<b>Oxoid Signal</b>	Thermo Fisher Scientific	Blood culture with media	Whole blood	24hr	Pathogen identification	Yes	Requires laboratory equipment
<b>Molecular Diagnostic Based</b>							
<b>QuickFISH/PNA FISH</b>	AdvanDx	Fluorescence in situ hybridization	Positive blood culture	~1.5 hr	Pathogen identification	Yes	Requires microarray equipment
<b>hepatoFISH</b>	Miacom diagnostics	Fluorescence in situ hybridization	Positive blood culture	0.5 hr	Pathogen identification	Yes	Requires microarray equipment
<b>Proved-IT / Verigene</b>	Luminex	PCR amplification and array detection	Positive blood culture	3.5 hr	Pathogen identification	No	Requires PCR equipment
<b>FilmArray</b>	Biofire Diagnostics	Real-time PCR	Positive blood culture	1hr	Pathogen identification	Yes	Requires FilmArray system
<b>HEPLEX</b>	BAG	Multiplex PCR with end point detection using an enzyme-linked sandwich assay in a microtiter plate	Positive blood culture	3 hr	Pathogen identification	No	Requires PCR and complex instrumentation
<b>ACCE-PROBE</b>	Gen-probe	Chemiluminescent DNA probes (rRNA)	Positive blood culture	3 hr	Pathogen identification	No	Requires PCR and complex instrumentation
<b>PLEX-ID BAC</b>	Abott	PCR amplification with Electropray ionization mass spectrometric analysis	Positive blood culture	6hr	Pathogen identification	No/CE marking	Requires PCR and complex instrumentation
<b>Septi SR</b>	Becton Dickinson	Multiplex PCR	Positive blood culture	3 hr	Pathogen identification	Yes	Requires PCR equipment
<b>StaphPlex</b>	Qiagen	PCR amplification and Array detection	Positive blood culture	5 hr	Pathogen identification	No	Requires PCR and complex instrumentation
<b>MALDI-TOF</b>	bioMérieux	Matrix assisted laser desorption	Positive blood culture	2hr	Pathogen identification	No	Requires complex instrumentation
<b>Magicplex</b>	Seegene	Multiplex PCR	Whole blood	3.5 hr	Pathogen identification	No	Requires PCR equipment
<b>SeptiFast</b>	Roche	Multiplex PCR	Whole blood	6 hr	Pathogen identification	Yes	Requires PCR equipment
<b>SeptiTest</b>	Molz, Germany	PCR and sequencing	Whole blood	8-12 hr	Pathogen identification	No	Requires PCR and complex instrumentation
<b>VYOO</b>	SIRS lab	Multiplex PCR and gel electrophoresis	Whole blood	8 hr	Pathogen identification	No	Requires PCR equipment
<b>Xpert MRSA/SA</b>	Cepheid	Real-time multiplex PCR	Whole blood	1hr	Pathogen identification	Yes	Requires PCR equipment

Device	Company	Technology	Sample	Turnaround time	Sepsis Diagnosis	FDA clearance	Point-of-care?
VAPChip	Eppendorf Array Technologies, Belgium	Multiplex PCR and hybridization	Whole blood	5–8 hr	Pathogen identification	No	Requires PCR and complex instrumentation
DiagCORE	STAT Diagnostics	48 plex real-time PCR	Whole blood	0.5–1.2 hr	Pathogen identification	No/CE marking	Requires PCR equipment
T2 Candida	T2 Biosystems, USA	Miniaturized magnetic resonance	Whole blood	3–5 hr	Pathogen identification	Yes	Requires complex instrumentation
<b>Pathogen Removal Devices</b>							
Cytosorb	Cytosorb	Removes cytokines with filter	Whole blood	Up to 24 hours a day, for up to 7 consecutive days	Bacterial removal	No/CE marking	Requires extracorporeal equipment with filtration in a hospital
LPSS Adsorber	Alteco Medical, Sweden	Peptide binding of endotoxin with porous polyethylene matrix	Whole blood	Not available	Bacterial removal	No/CE marking	Requires extracorporeal equipment with filtration in a hospital
LPS-binding for aramycin device	Spectral Medical	Ionic binding of Polymyxin-B and Lipid A to endotoxin	Whole blood	Recommended dosing: 2 hr hemoperfusion in 24 hr period	Bacterial removal	No/CE marking	Requires extracorporeal equipment with filtration in a hospital