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Nanotechnology in Sepsis: Diagnosis and Treatment Review

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Abstract – Sepsis is one of the main reasons of deaths internationally, with excessive mortality rates and a pathological complexity hindering early and correct diagnosis. Today, laboratory culture checks are the epitome of pathogen recognition in sepsis. However, their consistency stays a problem of controversy with false negative results frequently observed. Clinically used blood markers, C reactive protein (CRP) and procalcitonin (PCT) are indications of an acute-phase response and as a result lack specificity, supplying restrained diagnostic efficacy. In addition to bad diagnosis, inefficient drug delivery and the increasing prevalence of antibiotic-resistant microorganisms represent significant obstacles in antibiotic stewardship and hinder high quality therapy. These challenges have brought on the exploration for choice techniques that pursue accurate prognosis and high-quality treatment. Nanomaterials are examined for each diagnostic and therapeutic functions in sepsis. The nanoparticle (NP)-enabled seize of sepsis causative agents and/or sepsis biomarkers in biofluids can revolutionize sepsis diagnosis.

From the therapeutic factor of view, presently current nanoscale drug transport structures have established to be extraordinary allies in focused therapy, whilst many different nanotherapeutic functions are envisioned. Herein, the most applicable purposes of nanomedicine for the diagnosis, prognosis, and treatment of sepsis is reviewed, imparting a quintessential evaluation of their potentiality for scientific translation.

Keywords – Nanotechnology, sepsis, diagnosis, progression, therapy.

I. INTRODUCTION

Sepsis is described as “life-threatening organ dysfunction precipitated by a dysregulated host response to an infection.” [1] Today, sepsis is amongst the main motives of morbidity and mortality global in intensive care units (ICU) [1, 2] with its survival rate for extreme types reducing via as lots as 8% every hour [3] earlier than the suitable antibiotic therapy is initiated. [4]

Diagnosing sepsis as early as possible is seriously essential as delays in administering appropriate therapy can precipitously have an effect on outcome. Currently, diagnosis depends on clinical manifestations and blood exams for the detection of inflammation response-related blood biomarkers, such as CRP and PCT. These clinically available protein biomarkers however, lack specificity [5] making sepsis recognition in its early stages extraordinarily difficult. Microbiological culture methods continue to be the modern-day gold standard technique to become aware of causative pathogen phenotypes. Nonetheless, they can take up to 72 h and are frequently related with a high false negative rate.

Sepsis is a clinical emergency in which time is a vital factor. Delays in cure can lead to multiple organ failure and death. As such, due to the excessive mortality rate related with delayed therapy and the lack of specific diagnostic and therapeutic guidance, clinicians empirically administer broad-spectrum antibiotics as early as possible.[6] The use of broad-spectrum agents however,

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may additionally now not be as efficacious as therapeutics targeted towards particular pathogen phenotypes.[7] Another venture in the medical setting is the diagnostic uncertainty in differentiating septic patients from those struggling from non-infectious systemic inflammation. The clinical symptoms and signs of sepsis in its early stages simulate those of non-infectious infection and this leads to antibiotics being administered to patients with sterile infection or viral infections. The overuse of antibiotics is regularly related with undesirable side effects, such as the proliferation of antimicrobial resistant organisms and affected person toxicity. Moreover, as sepsis treatment is particularly restrained to antibiotics, clinicians depend on their therapeutic efficacy. Nevertheless, the acute changes in physiology all through sepsis can end result in poor pharmacokinetics and unsuccessful drug delivery. [8]

Considering all the pitfalls related with sepsis, there is a pressing need to strengthen rapid, sensitive and pathogen-specific detection tests, as properly as new antimicrobial strategies. Several promising aims have been proposed as workable capacity of sepsis detection and therapy, however they have been unable to step from research stage to medical implementation, due to difficulties in modelling the tremendously variable septic responses in preclinical systems.[9] Sepsis entails the activation of a mixture of one of a kind pathological pathways and consequently there are no accurately representative animal models that can reflect sepsis heterogeneity and sufficiently simulate its complexity.[9]

To date, there is a constrained portfolio of preclinical information displaying superior sensitivities and specificities when in contrast to clinically used technologies, and this poses tremendous challenges in clinical trials. [10]

The emergence of nanotechnology and its incorporation in medicine have revolutionized the regular pharmaceutical and clinical world.[11] The discipline has already proposed progressive technological options to enhance contemporary diagnostic and therapeutic administration of several pathologies.[12-16] Strikingly, even though nanotechnology counts solely various decades, greater than 200 nanomedicine constructs are underneath clinical investigation or clinical use.[17] The employment of nanoparticles (NPs) for diagnostic and therapeutic functions provides amazing potential, owing to their tunable properties (e.g., size, charge, surface chemistry, shape, and composition) and their potential for surface functionalization (with ligands, antibodies, and targeting molecules), which permits focused and selective binding. Additionally, nanoscale drug delivery structures can be engineered to enhance the biodistribution of already current therapeutics via enhancing the efficacy, steadiness and bioavailability of the drug at the target site. [18] All these together, have brought about the lookup for “Nano” techniques that should assist clinicians in addressing the major roadblocks related with sepsis.

This evaluation will spotlight the present day ultra-modern on novel nanotechnology-enabled techniques for the diagnosis, treatment, and monitoring of sepsis and will talk about the future improvement of superior and clinically relevant nanotheranostic platforms.

1. Nano diagnostic Technologies for Sepsis

Rapid, sensitive and specific detection of the infectious pathogen is fundamental for the medical development and result of a septic patient. Current molecular strategies employed for microbial infection diagnosis, consisting of enzyme-linked immunosorbent assay (ELISA) and polymerase chain response (PCR) are thought to provide excessive sensitivity and reproducibility. However, they require skilled personnel, pose an excessive risk of sample contamination and lack versatility needed in clinical diagnosis. [19]

Nanotechnology can resource in the improvement of fast, sensitive, and correct strategies for sepsis detection.[20, 21] Several NPs have been investigated to permit the diagnosis of sepsis-related microbial infections, such as magnetic (MNPs), gold (AuNPs), fluorescent (silica and quantum dots QDs), and lipid-based NPs.[22-26] Most of them are in particular used as distinction agents and biosensors to facilitate the detection of both proteins and nucleic acids related with sepsis (CRP, PCT, and miRNA), pathogenic DNA or bacterial cells by using amplifying signals. The foremost strategies studied for NP-enabled sepsis prognosis are primarily based on PCR, colorimetric biosensing, surface-enhanced Raman scattering (SERS), lens-free interferometric microscopy (LIM), mass spectrometry (MS), and magnetic resonance imaging (MRI) (Table 1, 2). Herein, we strictly focal point on the “Nano” diagnosis of sepsis and consequently of microbial infections brought on by way of positive pathogens (e.g., micro organism and fungi) which are often encountered in sepsis, such as Staphylococcus aureus, Klebsiella pneumoniae, and Escherichia coli, to identify however few.

1.1 Gold Nanoparticle (AuNP)-Enabled Sepsis Diagnosis

Within the subject of nanotechnology, AuNPs are substantially used and are especially eye-catching in diagnostics due to their facile chemical and tunable optical properties. The first-rate optical overall performance of AuNPs originates from their special interplay with light. The collective oscillation of electrons on AuNPs surface, regarded as localized surface plasmon resonance (LSPR), leads to an effective extinction of light. [27] The LSPR phenomenon is notably structured on the size, shape, surface chemistry, and aggregation state of AuNPs. For instance, spherical AuNPs with a suggest diameter ranging from 20 to a 100 nm exhibit a most absorbance from 520 to 570 nm, respectively, whereas these with sizes above 100 nm showcase broader absorbance peaks.[28] Apart from size, form additionally performs a crucial, with gold nanorods and nanostars being mainly alluring due to their height absorbance in the infra-red place of the spectra.[28] Moreover, upon aggregation, AuNPs exhibit a redshift in most absorption that can produce a colour alternate in the answer in which they are dispersed in. The reality that the optical properties of AuNPs can be without problems tuned by means of altering their physicochemical properties allows their exploitation for diagnostic applications. Furthermore, their ease of functionalization with focused on probes makes them best biosensors for the detection of infectious agents and different biomolecules. [29]

In view of the above, AuNP-enabled colorimetric biosensing of pathogens is amongst the most attractive applications. Mirkin et al., brought a novel sensing method to become aware of DNA sequences upon the self-assembly of AuNPs. [30] Non-complementary DNA oligonucleotides have been connected to the surface of AuNPs (13 nm in size). Once a duplex DNA, complementary to the DNA oligonucleotides connected to the AuNPs, used to be introduced to the solution, NPs self-assembled into aggregates. The interplay of capped-AuNPs with DNA caused a colour alternate in the solution, which ought to be tailor-made by way of varying the NPs measurement and the oligonucleotide sequence and length. [30] This find out about opened up a new pathway of DNA-NP hybrid substances with special and tunable optical properties. Inspired by using the above strategy, Elghanian et al., proposed a colorimetric approach to selectively observe precise polynucleotides by the use of mercaptoalkyloligonucleotide-functionalized AuNP (13 nm) probes. [31] Binding of AuNP probes to precise centred DNA sequences resulted in an awesome shift in AuNP SPR peak. Despite the simplicity of this strategy, the approach is limited by means of its fairly low restriction of detection (LOD: 10 fmol of target DNA). The above research catalysed the emergence of the future era NP-based systems for the speedy and sensitive colorimetric detection of pathogenic DNA in sepsis.

In a subsequent study, Storhoff et al., developed a “spot-and-read” colorimetric approach the use of DNA-modified AuNPs (50 nm) to swiftly observe precise mecA gene sequences of methicillin-resistant S. aureus strains.[32] Authors hypothesized that the use of higher AuNPs (50 nm) would end result in greater sensitivities in contrast to smaller AuNPs (13 nm), which have been used in preceding comparable studies.[30, 31] Interestingly, this approach confirmed greater sensitivity (333 zmol or 2×10^5 target molecules) in contrast to preceding studies[31,33] and enabled a detectable colour exchange in the samples options inside 2 h.[32]

Mirkin and Hill developed an in vitro ligand exchange bio-barcode assay for the detection of nucleic acid and protein biomarkers within 9–10 h. [34] Magnetic microparticles (MMPs) and oligonucleotide-functionalized 13 nm AuNPs probes, carrying thiolated single-stranded barcodes, have been combined and formed a sandwich round the target of interest. Barcodes had been then launched from the sandwich shape and hybridized.

The DNA barcodes have been detected the usage of oligonucleotide-conjugated AuNP probes with excessive sensitivity for numerous protein (10^{-18} M) and nucleic acid (10^{-19} M) targets. Based on this bio-barcode assay, Nanosphere, Inc. developed a FDA permitted test, the “Verigene,” to become aware of pathogens. In Verigene, silver-enhanced AuNPs (13–20 nm) enable the qualitative identification of Gram-positive bacteria and genes related with bacterial infection. [35] Each NP is functionalized with a described range of oligonucleotides, particular to a specific protein of interest. High specificity, amplified signal readouts, steadiness and decreased toxicity are the key property that led this assay to scalability and scientific applicability.

A rapid strain-specific detection technique used to be pronounced with the aid of Wang et al., the use of vancomycin-conjugated magnetic beads and nucleotide-labelled AuNPs probes. [36] Conjugated magnetic beads had been used to seize bacteria, whereas labelled AuNPs have been designed to feel and discover three distinctive bacterial sorts (E. coli, K. pneumonia, and S. aureus) through hybridization-induced coloration change. Bacterial samples had been coincubated with magnetic beads in a built-in microfluidic device to enable capturing. Addition of strain-specific AuNPs probes led to bacterial DNA hybridization, inducing accordingly shade exchange in the contaminated sample. Interestingly, the investigated bacterial traces had been detected within

25 min with capturing rates above 90%. Despite the promising effects of this technology, the selectivity of the described microfluidic chip in the presence of extra pathogens must be in addition explored.

More recently, a naked-eye detection approach of urease-positive microorganism the usage of magnetic beads and plasmonic AuNP sensors used to be proposed. [37] Following magnetic capturing of microorganism and urea addition in solution, the pH-dependent assembly of AuNPs triggered red- or blue-coloured NP suspensions, reflecting the presence or not, respectively, of urease-positive bacteria. As urease-negative microorganism did no longer increase the pH upon urea addition, the acidic conditions of solution led to AuNPs clustering and a blue coloured test. Conversely, urease-positive microorganism caused a rise in the pH of the solution due to NH3 manufacturing and avoided AuNPs clustering. The developed method enabled the ultrasensitive (10 CFU mL^{-1}, colony forming unit $mL^{-1)}$ detection of Proteus mirabilis in human urine samples inside 40 min.

In a later study about of the same group, carboxylate-, amine- and polyvinylpyrrolidone-coated AuNP probes had been exploited for the fast detection of interleukin-6 (IL-6) the use of a smartphone-based colorimetric device. [38] The developed nanoplatform entailed a paper-based biosensor coupled with a smartphone app for colorimetric sign quantification. AuNP probes have been immobilized onto the filter paper and the generated coloration used to be assessed with the customized designed cell app. The NP-enabled cellular biosensor enabled the sensitive detection of IL-6 in buffer solution and IL-6-spiked blood with 0.1 and 12.5 pg mL^{-1} LOD, respectively, inside 17 min.

A novel point-of-care system stimulated through lens-free interferometric microscopy (LIM) which encompasses a plasmonic Au nanohole substrate and customized bio printed microarrays used to be proposed through Dey et al., [39] Upon the incubation of plasma samples from wholesome donors, non-infectious systemic infection controls and sepsis patients onto the Au nanohole substrate, authors have been capable to optically become aware of E. coli with an LOD of 400 CFU mL−1. The LIM system used to be similarly developed to one at a time experience CRP, IL-6, and miRNA-16 biomarkers in spiked PBS samples. [40] Specific antibodies for the goals of pastime have been immobilized to the Au nanohole array chips and CRP, IL-6, and miRNA-16 markers had been quantified by way of the photonic biosensor with LOD of 18, 88, and 6 μg mL^{-1}, respectively.

Novel diffusometric DNA nanosensors, composed of 200 nm fluorescent polystyrene beads sandwiched with methicillin-resistant S. aureus and 80 nm AuNPs oligonucleotide probes, have been designed through Wang et al. to seize and expand respectively S. aureus DNA. [41] The sensing mechanism was once based totally on the NP size-dependent Brownian motion, via which any adjustments in NPs diameter ought to be reflected on diffusivity and measured. In the presence of bacterial DNA, the dimension of PS nanobeads increased, main to a limit in their Brownian action and as a consequence decrease diffusivity. The diffusometric DNA nanosensor allowed S. aureus DNA quantification with 10×10^{-12} M LOD.

1.2 Fluorescent Nanoparticle-Enabled Sepsis Diagnosis

Fluorescence-based methods are frequently utilized for the detection of pathogen-related molecules in microbial infections. Owing to their special fluorescent properties and greatest photo stability over traditional fluorophores, fluorescent NPs, such as QDs and silica NPs, enhances detection sensitivities. [22,42]

QDs are semiconducting nanocrystals with their measurement ranging between 2 and 10 nm and identifying the colour of the emitted light. Their size-dependent properties stem from the quantum confinement impact, which leads to the manufacturing of quite a number emission wavelength. This correlation between the measurement and the energy evils of QDs lets in their tunable manufacturing for a range of applications, which include bio imaging. [43] Furthermore, their special electrical and optical properties make them most suitable to traditional fluorophores. QDs have been determined to show off longer fluorescent lifetimes than typical fluorophores, [44] ensuing in accelerated sensitivities and signal readouts. [45] Silica NPs can be used in a variety of organic functions owing to their magnificent biocompatibility, thermal balance and low cytotoxicity. The improvement of mesoporous silica NPs in particular, with an intermediate pore measurement vary between 2 and 50 nm, has catalysed the evolution of new diagnostic possibilities. Their elevated photograph contrast, chemical stability, and controllable dimension with a slim distribution and their potential to conjugate with purposeful moieties inside the pores have established extraordinarily advisable for bio imaging and bio sensing. [46,47] Herein, we evaluation some examples of QD- and silica-based sensors for pathogen detection in sepsis.

For instance, mannose-modified fluorescent 3 nm carbon QDs (Man-CQDs) have been synthesized via Weng et al., to label E. coli. [48] Bacteria had been coincubated with Man-CQDs for 1 h and samples had been fluorescently characterized. Selective

binding of Man-CQDs to E. coli resulted in the emission of shiny blue fluorescence indicating the presence of the pathogen with a LOD of roughly 450 CFU mL^{-1}. The selectivity of this nanoplatform towards E. coli was once attributed to the unique interplay of mannose devices with the FimH lectin of E. coli. Subsequently, human urine samples spiked with E. coli have been incubated with Man-CQDs. The photo stability of the fabricated components and the special fluorescent properties of QDs enabled the successful labelling and detection of E. coli in all samples with a minimal detectable awareness of $\approx 10^3$ CFU mL^{-1}. Even though, the proposed technique is promising, in addition optimization is required in order to gain greater sensitivities and discover pathogens in a much lower concentration.

Recently, green and red emitting QDs (CdSe-QDs) have been employed to permit the simultaneous labelling and quantification of CRP and IL-6 biomarkers by means of a point-of-care lateral go with the flow assay (LFA). [49] A custom-made software program tool, the MultiFlow-Shiny app, used to be used to manner and analyse the LFA experimental data. By a single UV-light source, each CRP and IL-6 have been quantified with $42.5 \times 42.5 \times 10^{-9}$ and 0.21×10^{-12} M detection limits, respectively, values which are inside the medical vary discovered in sepsis.

Using antibody-bio conjugated silica NPs (60 nm) encapsulated with fluorescent dye molecules, Zhao et al., efficiently detected single bacterial cells inside 20 min. [50] Thousands of dye molecules had been encapsulated in every silica NP and substantially contributed in signal amplification, enabling ultrasensitive quantitation of pathogenic targets. This approach used to be because of this employed to concurrently discover more than one bacterial species (E. coli, S. aureus, and S. typhimurium). [51] Multi-coloured silica NPs had been conjugated to monoclonal targeted antibodies specific to these pathogens and facilitated a multiple of micro-organism detection.

Similarly, a quick and sensitive assay for S. aureus detection was once developed through Borsa et al., the usage of aptamer-functionalized silica MNPs (187 nm) and fluorophore-loaded biosensors made from silica NPs, known as “Nanokeepers,” specific to micrococcal nuclease (MNase). [52] MNase is the most widespread biomarker for S. aureus, as it is naturally secreted from bacterial cells. Blood samples spiked with 102 CFU mL−1 S. aureus had been incubated with functionalized silica MNPs to seize bacterial cells by using magnetic pulldown. Approximately 61% of bacterial cells have been efficiently captured from entire blood. Subsequent heating led to MNase launch into the solution, in which Nanokeepers had been added. Nanokeepers notably greater the fluorescence signal and enabled the sensitive detection of S. aureus in the samples. Interestingly, the fluorescence signal used to be amplified as the wide variety of S. aureus cells was once growing ($>10^5$ cells mL^{-1}), whilst the LOD was once calculated at 682 cells mL−1, which is promising and requires in addition investigation.

1.3 Magnetic Nanoparticle (MNP)-Enabled Sepsis Diagnosis

A range of modern functions has been emerged making use of MNPs. MNPs are some ways extra inclined to exterior magnetic fields than bulk substances and this stems from the greater range of electrons that spin in the identical direction. Additionally, magnetic discipline power is size-dependent. [11] For instance, iron oxide NPs smaller than 20 nm, acknowledged as superparamagnetic iron oxide NPs (SPIONs), have a single area of electrons that spin in the identical direction, whilst iron oxide particles with diameter higher than 20 nm have more than one domains of electrons that spin in contrary instructions. Therefore, SPIONs provide greater magnetic liability to exterior magnetic field than different paramagnetic materials. [11] Another asset of SPIONs is demagnetization as soon as the exterior magnetic field is removed, which is very necessary for biomedical applications. Several MNPs, specially SPIONs, have been FDA authorized and are presently used as contrast agents for MRI, [53,54] and this makes them very alluring to help in sepsis diagnosis.

In this context, Neely et al., developed a T2MR (T2 magnetic resonance) diagnostic platform the use of oligonucleotide probes for Candidemia embellished with SPIONs (800 nm). [55] The SPION-based biosensor enabled the ultrahigh sensitive (≈1–3 CFU mL^{-1}) detection of 5 clinically frequent Candida species in complete blood within 3 h. SPIONs had been covalently conjugated with oligonucleotides to generate 2 populations of probes, every of them carrying a target-complementary probe. Blood spiked with Candida and unknown scientific samples have been incubated with SPIONs. Hybridization of DNA targets led to the formation of SPION clusters with the clustering degree reflecting the DNA concentration. The amplified Candida DNA was once then measured through PCR producing T2MR signals. Strikingly, the T2MR biosensor fashioned the groundwork for the layout of a computerized instrument platform. “T2Candida panel,” as the pathogen detection nanoplatform used to be later called, has been FDA approved, facilitating direct and fast evaluation of complete blood specimens for the identification of 5 Candida species barring any requirement for blood culture. Results from the first sizeable multicentre scientific trials of T2Candida panel

confirmed an average specificity and sensitivity per affected person of 98.1% and 91.0%, respectively, with a common time to species identification of 3 to 5 h. [56, 57]

Simplicity, low-cost, single-cell detection accuracy, minimal pattern processing and quickly assay time are essential elements for an effective diagnostic device with scientific potential. In admire of this, Issadore et al., developed a transportable microfluidic chip-based micro-Hall (μHall) platform for sturdy and high-throughput (10^7 CFU/min) bacterial detection. [58] Targeted microorganism have been labelled with the aid of MNPs and had been rapidly detected with the aid of the miniaturized μHall device.

In some other study, Chung et al., described the plan of 20 nm Nano magneto-DNA probes to unexpectedly and sensitively profile a variety of pathogens in medical samples through focused on the bacterial 16S ribosomal RNA vicinity.[59] Although this rRNA place is constant between all bacteria, it is characterised by means of species-associated variabilities in distinct areas of the genetic sequence and can consequently enable big difference between bacterial types.[60] Combination of the oligonucleotide–MNP probes with a miniaturized micro nuclear magnetic resonance machine for signal readout[61] enabled the correct detection and phenotype of a large pool of 13 distinct bacterial species within 2 h with a 0.5×10^{-12} M LOD.[59]

A surface-enhanced Raman scattering (SERS)-based assay used to be developed via Nguyen et al. to screen a triplex panel of sepsis protein biomarkers: CRP, PCT, and sTREM-1. [62] Mesoporous silica templates have been synthesized with magnetic immune colloids to anchor 20 nm antibody-coated Au-coated MNPs. Fabrication of these SERS substrates improved Raman signal and catalysed the detection of CRP, PCT, and sTREM-1 biomarkers in human serum samples with LOD values being noticeably low at 27, 103, and 78×10^{-12} for CRP, PCT, and sTREM-1, respectively.

Another fascinating SERS-based approach proposed the use of biomimetic octopus-like NPs with a magnetic core and an adorned with aptamers polymeric multi-arm shell to particularly seize and become aware of S. aureus amongst a pool of 4 pathogens. [63] The polymeric palms and the multivalent ligands laboured synergistically, imitating the suction cups of an octopus, to decorate bacterial attachment and seize with excessive sensitivity (10 CFU mL^{-1}).

During sepsis, the stimulation of host immunity triggers the immoderate manufacturing of reactive oxygen species (ROS) in the blood circulation and affected organs, and as a consequence ROS have been then again regarded as sepsis biomarkers. On the grounds of this, the clinically authorized gadolinium-diethylenediamine penta-acetic acid (Gd-DTPA) with an hyaluronic acid (HA)-decorated iron oxide core (SPIONs) was once these days employed as a distinction agent to probe ROS via MRI in an lipopolysaccharide (LPS)-induced sepsis mouse model.[64] The limitless tissue penetration depth of SPION Nano probes accompanied with the HA-triggered ROS degradation mechanism and the subsequent launch of Gd-DTPA enabled ultrasensitive (0.2×10^{-6} M) ROS imaging in vivo.

MNPs can additionally be used as affinity probes to selectively trap infectious agents and enrich their low attention degrees from a complicated organic matrix. These nanoscale probes can decorate the sensitivity of proteomic methods through casting off the obstructive signal interference from different biomolecules.[26]Recently, Hasan et al. employed MNPs (<15 nm) modified with 3-aminopropyltriethoxysilane to enable interplay with β-lactam antibiotic amoxicillin and efficaciously observe S. aureus and E. coli with the aid of matrix-assisted laser desorption–ionization (MALDI-MS).[65] Penicillin binding proteins (PBPs) naturally contained in microorganism had been certain to amoxicillin functionalized MNPs. Subsequently, MALDI-MS was once carried out to comprehensively analyse the connected PBPs onto the floor of MNPs. Both bacterial MALDI mass spectra have been extensively enriched with PBPs, owing to the excessive affinity of amoxicillin engineered MNPs for β-lactam. Noteworthy, the lowest detectable concentrations for each S. aureus and E. coli had been ranging between 10^3 and 10^4 CFU $mL^{-1.}$ [65]

1.4 Liposome-Enabled Sepsis Diagnosis

Apart from boosting the indicators of diagnostic assays concentrated on unique and already acknowledged biomolecules, NPs can be additionally used for the gain of novel biomarkers discovery. Particularly interesting is the currently recommended thinking of exploiting the NP–protein corona, a layer of proteins adsorbed onto NPs floor as soon as in contact with bio fluids, to harvest disease-specific, beforehand unknown biomarker proteins via excessive throughput label-free MS. Triggered by using the preliminary concept of the “personalized protein corona”,[66] the use of the NP–protein corona fingerprinting to differentiate between wholesome and unhealthy samples stimulated a collection of investigations.[67-72]In one of these studies, polyethylene glycol functionalized liposomes have been injected into the blood circulation of tumour-bearing mice and as a result recovered to

signify the in vivo shaped protein corona by using liquid chromatography-MS (LC-MS/MS). Authors validated that the liposomes enabled the seize and amplification of low molecular weight and low plentiful proteins from the blood circulation of tumour-bearing mice, which ought to no longer be detected by way of traditional proteomics.

In the context of sepsis, Papafilippou et al., proposed the use of liposomes as blood sepsis-specific protein scavengers. [70] Commercially on hand amphotericin B-containing liposomes (AmBisome, one hundred nm) have been incubated with plasma samples received from sepsis and non-infectious acute systemic infection patients, and the resultant protein coronas had been totally in contrast by using LC-MS/MS. The proteomic evaluation of liposome-corona fingerprints printed 67 differentially expressed proteins between sepsis and non-infectious acute systemic inflammation, with 9 out of these 67 being earlier related with bacterial contamination pathways. This work furnished proof that NP-enabled MS evaluation can find panels of novel protein biomarkers for sepsis which would in any other case be undetectable.

2. Nano monitoring for Sepsis Progression

Antimicrobial susceptibility evaluation is quintessential for the administration of sepsis. The improvement of multidrug resistance (MDR) mechanisms with the aid of micro-organism hinders antibiotic stewardship decision. Assays in a position to examine microbial sustainability antibiotic and efficacy can information clinicians with remedy choice making and optimization of the antibiotic concentration, dose and administration frequency. [73] In view of the above, countless Nano-based applied sciences that can decide the antimicrobial susceptibility in actual time have been developed. Here, we existing some of the most applicable for sepsis.

Nath et al. mentioned an antimicrobial susceptibility assay the use of dextran-coated AuNPs (25 nm) that shaped nanoclusters in the presence of concanavalin A (Con A), a protein with excessive affinity to carbohydrates in bacterial suspension. [74] In order to investigate the bacterial metabolic activity, the floor plasmon bands of AuNPs had been profiled following their incubation with E. coli (10^6CFU $mL^{-1)}$. Upon bacterial growth, carbohydrates had been unexpectedly consumed and their quantity in the medium decreased. Consequently, AuNPs shaped small gold nanoclusters with decrease plasmon resonances. Under bacterial boom inhibition, the presence of free carbohydrates, and consequently Con A, prompted the massive self-assembly of AuNPs, ensuing in an enormous redshift of the NPs floor plasmon band. This nanoplatform enabled the sensitive evaluation of bacterial proliferation within 3 h. However, as microorganisms in most of sepsis instances are existing in the blood of contaminated patients, trying out bacterial susceptibility in blood- or urine-containing media alternatively than bacterial media would be extra representative of the real-life conditions system.

This thought used to be in addition investigated via Kaittanis et al., [75] who evaluated the bacterial metabolic activity and antimicrobial susceptibility in blood even at low populations (10^2–10^4 CFU mL^{-1}) by water relaxation using both dextran- or Con A-conjugated SPION-based nanosensors. At low bacterial growth and minimal metabolic activity, polysaccharides availability prompted the formation of massive nanoclusters main to great alternate in spin–spin rest time of the solution's water protons. The consumption rate of vitamins used to be measured inside 2.5 h and 5 min through dextran- and CoA-coated SPIONs, respectively. [75] This NMR-based strategy enabled speedy profiling of bacterial responses and eradicated the difficulty of robust media absorbance which is often discovered in optical-based assays.

Evaluating immune system responses may want to additionally allow sepsis development monitoring. Using the FDA-approved SPION-based contrasts agents “Feridex,” Wong et al., monitored the immune system activity in vitro and in vivo and especially Kupffer cells. [76] Once Kupffer cells experience an ongoing infection, they rapidly multiply. Meanwhile, the dominant mechanism through which Feridex is cleared from the physique is phagocytosis by using Kupffer cells.[77] It was once for that reason hypothesized that excessive Feridex uptake activity would replicate excessive stages of Kupffer cells, indicating an alert immune system due to workable infection.[76] Mapping of Feridex NPs uptake by using MRI in E. coli derived LPS-induced murine monocytes and sepsis mouse models printed the approximate quantity of launched Kupffer cells. LPS-treated cells displayed a greater NP uptake than non-LPS cells. Moreover, greater stages of iron internalization in the LPS-treated monocytes in contrast to the untreated indicated an accelerated phagocytic activity. Although substantial variations have been discovered in Feridex uptake in vitro, no variations had been proven in vivo. However, this used to be a pilot learn about and in addition work is required to discover the position of Kupffer cells in sepsis.

3. Therapeutics

The mainstay of remedy in sepsis revolves round two vast principles: (1) supply manipulate to take away the infectious stimulus and (2) resuscitation optimization to each attenuate the pathologic inflammatory response and furnish end-organ support. Current supply manages healing procedures encompass antimicrobial administration and procedural interventions to decrease the pathogenic burden [78]. Unfortunately, these treatments incompletely tackle the critical position of infectious molecular triggers to incite and propagate the attribute inflammatory cascade of sepsis that manifests itself to exclusive stages in accordance to every patient's special immune system and biochemical milieu. Meanwhile, supportive care is frequently restrained to the implementation and titration of treatment plans such as intravenous fluids, vasopressors, mechanical ventilation, and renal alternative remedy (RRT). Comprehensive software of the right aggregate of the above healing procedures in a well-timed manner improves effects in sepsis. We talk about novel cures (Table 3) that goal the pathogen burden and these that goal the host through attenuating the negative results of the molecular triggers of infection to guide patients till recovery.

3.1 Pathogen-Directed Therapies

3.1.1 Pathogen-Associated Molecular Pattern Removal Devices

Pathogen-associated molecular patterns (PAMPs) set off immune cells to launch pro-inflammatory mediators that can set off the dysregulated inflammatory response in sepsis. The appealing factor of filters concentrated on PAMP removal, as adverse to imposing techniques that goal particular cytokine elimination deactivation, is the potential to dispose of upstream triggers of infection in lieu of trying to right the downstream and less understood milieu of both good and bad inflammatory markers. Several promising devices get rid of PAMPs the usage of extracorporeal hemofiltration devices, frequently in conjunction with both RRT or extracorporeal membrane oxygenation. Due to developing concerns about the consequences for multidrug-resistant (MDR) pathogens, the Defence Advanced Research Projects Agency (DARPA) has furnished large investments to make expand this field.

The GARNET device, created via BOA Biomedical, is an extracorporeal hemofiltration system that makes use of the Fc-mannose-binding lectin (FcMBL) connected to fibres inside a hole cartridge. FcMBL is created from the Fc element of human immunoglobulin, which is connected to a carbohydrate recognition domain of mannose-binding lectin (MBL) [91]. MBL, a blood opsonin, can recognise and bind an extensive vary of PAMPs. FcMBL is capable of binding 85% of isolates from 97 of 112 (87%) pathogen species, consisting of the most frequent pathogens accountable for sepsis, and a vast vary of bacteria, parasites, and viral antigens [95]. A preclinical trial in rats confirmed a >90% limit in bacterial load and accelerated survival after 5 hours of use [92]. Patients are presently being enrolled in a multicentre trial the usage of the BOA Biomedical machine [79].

The hemofiltration device Seraph-100, produced by way of ExThera, makes use of heparin sulfate-coated absorption beads inside a cartridge to bind and sequester pathogens. In a case study, hemofiltration the usage of this gadget diminished the bacterial load of Staphylococcus aureus. Following case research demonstrating accelerated hemodynamics with its use, Seraph-100 used to be authorised for use in the European Union and obtained emergency use authorization (EUA) for the remedy of extreme Covid-19 by way of the Food and Drug Administration (FDA) [93].

Oxiris, owned with the aid of Baxter, is an adsorptive membrane with a negatively charged, microporous structure created to eliminate cytokines and endotoxins in the course of RRT. Its use in sepsis, when in contrast to historic controls, reduces SOFA ratings by using 37% at 48 h [94]. Due to its capacity to minimize serum IL-6 levels, it acquired an EUA from the FDA for use in severely unwell Covid-19 patients.

Another promising device, Cytosorb, is a hemofiltration system created with biocompatible polystyrene divinylbenzene copolymer beads. It clears each pro-inflammatory cytokines and PAMPs however is unable to clear endotoxins [94,95]. Its use reduced IL-6 stages and mortality in one observational learn about of septic patients on non-stop RRT; however, the solely RCT achieved stated no enormous exchange in IL-6 levels, SOFA scores, or mortality [94,96]. This might also be due to the particularly quick (6 h) day by day remedy administered. It has obtained an EUA for use in the placing of Covid-19 accompanied by means of extended cytokines.

Two different adsorption devices, Toraymyxin and Alteco LPS, particularly goal endotoxin removal. Toraymyxin is permitted for use in Japan to deal with patients with gram-negative bacterial infection, on the other hand no randomized managed trials (RCTs) have proven reduced mortality for endotoxin clearance by alone [94]. The Alteco LPS device, however, verified an enhancement

in patients' hemodynamic [94]. While PAMP elimination technological is promising and ongoing trials may additionally reveal usefulness, FDA approval does no longer but exist for its use in sepsis [88,96].

3.1.2 Bacteriophages

Phage remedy has experienced renewed activity in current years due to the emergence of MDR micro-organism [80]. Bacteriophages are possible alternatives to antibiotics given their potential to cleave capsular polysaccharides on organisms such as Klebsiella pneumoniae [97]. Murine models of sepsis tested that a single dose of the studied phage protected 80–100% of subjects against death [97]. Additionally, case reviews report precise consequences ensuing from the use of bacteriophages in human patients with recalcitrant and pan-resistant gram-negative bacteraemia [98].

3.1.3 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is an infusion of pooled IgG immunoglobulins that pursuits a number of organisms or inflammatory conditions, which include Guillain–Barre syndrome, immune thrombocytopenic purpura, and Kawasaki disorder [96]. IVIG has been used in sepsis to each inhibit the inflammatory response and to opsonize the offending infectious agent. Data are inconclusive concerning its efficacy in sepsis and is presently now not advocated for routine use [81,88]. However, a latest meta-analysis of IV IgM infusions displaying decreased mortality in those with septic shock has renewed pastime in this remedy [99].

3.1.4 Targeted Monoclonal Antibodies

Direct antibacterial antibodies focused on Pseudomonas aeruginosa and Staphylococcus aureus are present process scientific trials [81]. Two monoclonal antibodies towards Staphylococcus aureus toxin, suvratoxumab and AR-301, exist. Suvratoxumab reduces disease severity in mice and has gone through phase 2 trial which showed a trend towards decreased incidence of Staphylococcus aureus pneumonia when used pre-emptively in excessive risk, routinely ventilated ICU sufferers [100]. AR-301, in a segment two trial, confirmed a vogue toward quicker decision of pneumonia in these with extreme Staphylococcus aureus hospital-acquired pneumonia, ventilator-associated pneumonia, or community-acquired pneumonia [101]. A phase 3 trial is presently underway [81].

3.1.5 Liposomes

Many micro-organism secrete toxins that injury cellular structures. Artificial liposomes, which can bind and sequester these toxins [102], have proven elevated survival in mice with Streptococcus pneumonia septicaemia [81]. When in contrast to controls, CAL02, one such agent, confirmed a reduction in organ dysfunction scores in 19 patients admitted to an intensive care unit for severe pneumococcal pneumonia [82].

3.1.6 Alkaline Phosphatase

Sepsis-mediated acute kidney injury causes renal cell apoptosis and will increase the chance of mortality and development to end-stage kidney disease [81]. Alkaline phosphatase protects in against renal inflammation via deactivating bacterial LPS [81]. A phase 2 study about in patients with sepsis-induced acute kidney injury verified a measurable improvement in renal feature in those with shock [103]. Large phase 2 researchs additionally referred to an improved creatinine clearance three to four weeks after randomization, as properly as a statistically substantial reduce in mortality [83].

3.1.7 Antimicrobial Peptides

Antimicrobial peptides (AMPs) are small proteins which belong to the innate immune system and have strong antibacterial, antiviral, and antifungal activity [104,105]. They feature in three distinct ways: 1) direct antimicrobial activity on target cell membrane, 2) antimicrobial endeavour through immune modulation, and 3) inhibition of bacterial intracellular characteristic [101]. Concerns of concomitant host cytotoxicity due to minimal specificity exist, although latest proof suggests that AMPs are functionally numerous in their goals [104,105]. Administration of AMPS concomitantly with antimicrobials can also be synergistic and limit affected person toxicity [104,105]. AMPs are presently present process segment three medical trials in extreme sepsis [84].

3.1.8 Nanoparticles

Nanoparticles incorporate a rapidly developing subject of research devoted to sepsis therapeutics. These engineered cures target specific microbes to both enhance the efficiency of systemic antimicrobials and reduce their side effects [85]. By directly concentrated on infectious organisms and neutralizing endotoxin, they additionally can also decrease rising antimicrobial resistance [85]. For example, the commercially accessible liposomal components of amphotericin B is a drug delivery Nano system integrated into a lipid bilayer that is only released on exposure to the targeted fungus, for that reason lowering the toxicity historically skilled with before formulations of amphotericin B [85]. Another Nano medicine loaded with ciprofloxacin binds endotoxins the use of nanostructures to neutralize bacterial LPS [85]. Early animal research has proven lowered cytokine ranges in these administered this therapy. In a murine study, lipid nanomaterials handing over mRNA encoding antimicrobial proteins augmented macrophages' capacity to eliminate MDR micro-organism [106]. This promising technological is expected to yield further advances in sepsis therapeutics.

3.2 Host-Directed Therapies

3.2.1 Angiotensin 2

Angiotensin 2, authorized by using the FDA in 2018, is the most up-to-date handy vasopressor for the therapy of vasodilatory shock. Angiotensin 2, a naturally occurring hormone in the body, is the end product of the renin–angiotensin–aldosterone system. It causes smooth muscle contraction and releases ADH. In the sitting of excessive dose vasopressors, exogenously administered artificial angiotensin 2 appreciably expanded suggest arterial strain (MAP), lowered vasopressor dose, and diminished sequential organ failure evaluation (SOFA) ratings in patients with refractory septic shock [107]. In these with an absolute or functional deficiency of angiotensin-converting enzyme, manifested by using a ratio of angiotensin 1/angiotensin 2 of ≥ 1.63 or multiplied renin levels, angiotensin 2 supplementation statistically notably accelerated survival [108,109]. This vasopressor suggests promising outcomes in conditions, such as ARDS, influenza, pneumonia, cirrhosis, acute kidney injury requiring renal substitute therapy, respiratory failure requiring veno-venous extracorporeal membrane oxygenation, post-cardiopulmonary bypass, cardiac arrest, and Covid-19-induced shock [110-116].

3.2.2 Selepressin

Selepressin, a vasopressin analogue extraordinarily selective for the V1a receptor, targets each V1a and V2 receptors. In experimental studies, selepressin decreases microvascular leakage and will increase mean arterial pressure (MAP) at decrease doses than vasopressin [117]. A promising phase2 a RCT verified that its use to be related with decreased doses of norepinephrine, much less fluid administration, and shorter period of mechanical air flow [118]. A subsequent phase2b/3 RCT demonstrated a greater MAP, decrease norepinephrine requirement, and decrease net fluid stability in the selepressin group, however it did no longer affirm a distinction in ventilator-free days or mortality [86]. Due to its lack of catecholaminergic stimulation, selepressin might also be in particular beneficial in patients with concomitant tach dysrhythmias [81]. This agent is now not authorized by means of the US FDA currently.

3.2.3 Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) can radically change to substitute damaged or destroyed cells [119]. These pluripotent mesenchymal stem cells have been proven to decrease injury and mortality in animal models of sepsis by using restoring endothelial barrier characteristic and bettering tissue restore [119]. Two ongoing phase 2 trials are evaluating the impact of MSCs on organ failure in patients with septic shock and extreme community acquired pneumonia [81,118]. Despite early promising data, issues exist about the potential for MSCs to become oncogenic, as these cell types have been recognized in tumours such as gastric adenocarcinomas, lipomas, and osteosarcomas [121].

3.2.4 Extracellular Vesicles

Extracellular vesicles (EVs) are a team of membrane-enclosed particles launched from cells involved in intercellular communication [120]. These vesicles transport RNA and proteins that modulate the immune response of lymphocytes [119]. With comparable properties to MSCs, EVs appear to show most reliable safety [120]. RNA and proteins delivered via EVs play a distinguished function in angiogenesis, apoptosis, and immune response whilst defending in opposition to sepsis-induced organ dysfunction [119]. Murine models spotlight its potential to attenuate bacterial pneumonia by means of enhancing macrophage

phagocytosis [121] and enhance renal healing for sepsis-induced acute kidney injury [122]. These findings have translated efficiently to patients with persistent kidney disorder via enhancing glomerular filtration rate [123]. Challenges continue to be in keeping apart MSC–EVs, and no present day standardized protocol for developing or naming EVs exists [120].

3.2.5 Toll-Like Receptor Ligand Binders

Immune cells categorical toll-like receptors that launch cytokines such as tumour necrosis factor-α and IL-6 to result in a strong innate immune response [96]. Binding TLRs should attenuate the immune response in these with sepsis; however, some specialists have expressed difficulty that interfering with this pathway ought to reason autoimmune, cardiovascular, neurological, and oncogenic problems [87]. While TLR agonists have verified therapeutic promise in most cancers immunotherapy [81], their antagonists have been used to efficiently deal with polymicrobial sepsis in mice [124]. Though the TLR4 antagonist Eritoran did now not exhibit a mortality advantage in patients with extreme sepsis, its indirect mechanism of endotoxin inhibition can also play a greater focused function in these with accelerated endotoxin stages [125]. A direct antagonist anti-TLR4 monoclonal antibody has been developed to deal with rheumatoid arthritis and can also be a rewarding goal for further investigation in those with sepsis [87].

3.2.6 Interleukin Agonists and Antagonists

Immune modulation the usage of each interleukin agonists and antagonists have been studied in the remedy of sepsis [117].

Although interleukins make contributions to host protection in opposition to infections [126], exaggerated synthesis of IL-6 can reason an acute extreme systemic inflammatory response recognized as cytokine storm or cytokine-release syndrome [126]. Prior to Covid-19, IL-6 receptor (IL-6R)-targeted agents (e.g., tocilizumab, sarilumab) have been used in general to deal with a variety of autoimmune problems such as rheumatoid arthritis [117]. While latest randomized manage trial of tocilizumab have suggested favourable responses in patients with Covid-19 pneumonia [118], the facts are inconsistent [119], and their therapeutic function for Covid-19 stays unclear. In addition, extra than 20 medical research are presently registered on ClinicalTrials.gov (accessed on 12 January 2020) that intention to consider the efficacy of monoclonal antibodies in opposition to IL-6 (e.g., siltuximab, sirukumab, olokizumab, clazakizumab) in Covid-19-induced sepsis and septic shock [89]. Debate surrounds the feasible accelerated infectious risks related with treatment options like IL-6- or IL-6R-targeted marketers [130,131]; however, findings from these ongoing research will make bigger the grasp of possible scientific functions of IL-6 pathway inhibition to non-Covid-19 sepsis as well.

Interleukin-7 (IL-7) is a cytokine that reverses sepsis-induced lymphopenia, prevents apoptosis, and induces T cell proliferation [132-134]. It has been proven to prevent death in animal models with abdominal infection due to Pseudomonas aeruginosa [135]. In a section two trial, administration of IL-7 accelerated absolute lymphocyte count barring worsening infection in those with septic shock [134].

While administration a recombinant IL-1 receptor antagonist did no longer enhance survival in sepsis, Anakinra, a recombinant IL-1R antagonist which blocks IL-1 release, reduces mortality in septic patients with markedly increased IL-1RA levels [136,137]. The inability to determine IL-1 levels limits its broad application to patients with sepsis; however, ongoing phase 2 trials predicted to end result in the coming 12 months have to similarly elucidate treasured statistics to be received on the matter [81].

3.2.7 Cyclic GMP-AMP synthase-stimulator of interferon genes (cGas-STING)

When brought on by using PAMP recognition, the cGas-STING pathway in the innate immune system potently prompts the inflammatory response [88]. Ceritinib, an FDA-approved drug for use in non-small cell lung cancer, targets this pathway. Despite no present day human trials in septic patients, concentrated on this pathway in murine models of sepsis prompted with cecal ligation and puncture tested a survival gain [138].

3.2.8 Adrenomedullin (ADM)

Sepsis motives endothelial dysfunction that consequences in vascular leak, thrombosis, and organ dysfunction [85]. Adrenomedullin counteracts this by using stimulating ADM receptors which then preserve the endothelial barrier and reduce irritation [96,139]. Adrecizumab is a monoclonal antibody that objectives anti-ADM antibodies and prolongs the half-life of ADM [93]. Because preclinical trials have proven promise in limiting endothelial injury and the remedy seems protected in phase

1 trials [140], a phase 2 RCT is presently underway [140]. As ADM also motives systemic vasodilation, its modulation in the sitting of septic shock might also restrict its utility [96].

3.2.9 Eculizumab

Sepsis-induced complement activation contributes to tissue injury and organ dysfunction [96]. Therapies focused on complement and its uncontrolled activation throughout sepsis have been efficiently studied in baboons and resulted in improvements in defects of coagulation and multisystem organ characteristic [141]. Eculuzimab, an FDA-approved monoclonal Ab concentrated on C5a for a typical haemolytic uremic syndrome, is presently being studied in phase 2 trials for patients with Covid-19-induced sepsis [142].

3.2.10 Interferon Gamma

Interferon gamma (IFN-ɣ) will increase tumour necrosis component manufacturing in patients with sepsis [143]. Though FDA-approved to deal with positive malignancies and persistent granulomatous disease by means of promoting pro-inflammatory cytokine release, case sequence documenting IFN-ɣ infusions in patients with fungal sepsis established enchantment in laboratory information and protection [144,145]. Despite preclinical facts suggesting a gain in sepsis, no posted RCTs have evaluated IFN-ɣ for this cause [145].

3.2.11 Triggering Receptor Expressed on Myeloid Cells-1 and Nangibotide

TREM-1 is a receptor expressed on monocytes and neutrophils that, when activated, triggers systemic inflammation [81]. Nangibotide is a TREM-1 antagonist that inhibits the overactive infection that can accompany infection [146,147]. In phase 1 trials, nangibotide was once discovered to be safe, even though established a very brief half-life of ~3 min [147]. In a follow up phase 2 trial in patients with septic shock, the nangibotide group had reduced SOFA scores with this model being even greater said in these with extended soluble TREM-1 tiers [90].

3.2.12 Immune Checkpoint Modulators

T cells are inhibited when programmed cell death ligands 1 (PD-L1) and 2 (PD-L2) bind the programmed cell death-1 (PD-1) receptor expressed on their surface [81]. Patients with sepsis have expanded PD-1 and PD-L1 expression, which correlates with expanded mortality [148]. Nivolumab, a monoclonal antibody directed towards PD-1 which prevents binding of PD-1/PD-L1, enhances IFN-ɣ manufacturing inducing an immune system response to infection [149]. Inhibiting PD-1, PD-L1, and cytotoxic T-lymphocyte antigen-4, a stimulatory molecule that is upregulated and suppresses T cell function in sepsis, improves survival in murine models of fungal sepsis [150]. In phase 1 and 2 trials, nivolumab used to be proven to be protected and accelerated absolute lymphocyte count number (ALC) in patients with vasopressor-dependent sepsis and low ALC [151].

3.2.13 Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the manufacturing of neutrophils and macrophages in the bone marrow. Administration of GM-CSF promotes immune reconstitution to combat infection and minimize the time to infection resolution [152]. GM-CSF is predominantly used in patients at elevated chance of infection due to chemotherapy-induced neutropenia. In an RCT of patients with sepsis-associated immune suppression, GM-CSF administration considerably reduced the length of mechanical ventilation [153].

II. Conclusion

Many novel and promising diagnostics and therapeutics are being developed to aid in the management of septic patients. Improved diagnostics will allow earlier diagnosis of sepsis, assisting to characterize both infecting organisms and pathways that become dysfunctional at some stage in sepsis. Despite enormous development in our understanding of the pathophysiology of sepsis, no single sepsis biomarker has but to address all diagnostic needs. Although combining multiple biomarkers with medical scoring structures may additionally outperform any single tool, these practices ought to additionally be validated in scientific practice. The wide adoption of diagnostic sepsis biomarkers has been hampered by means of each the lack of a gold standard for diagnosing sepsis and inherent study limits (e.g., size, design, medical applicability). Further investigations of suitable specimens, trying out assays, and cut-off levels for particular biomarkers are wished prior to large-scale integration into scientific selection making.

While in further evidence is needed prior to wide adoption of novel therapeutics, their addition to modern management has the practicable to revolutionize sepsis care. Rapidly focused on antimicrobial therapy to particular pathogens, moving the inciting infection stimulus, and personalizing therapies in accordance to every individual's inflammatory response and sepsis phenotype ought to herald a new era of increased clinical outcomes in patients with sepsis.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Authors have equally participated and shared every item of the work.

ABBREVIATIONS:

(CRP): C reactive protein.

(PCT): procalcitonin.

(ELISA): enzyme-linked immunosorbent assay.

(PCR): polymerase chain response

(ELISA): enzyme-linked immunosorbent assay.

(MNPs): magnetic nanoparticles.

(AuNPs): gold nanoparticles.

QDs: quantum dots.

(SERS): surface-enhanced Raman scattering.

(LIM): lens-free interferometric microscopy.

(MS): mass spectrometry.

(LSPR): localized surface Plasmon resonance.

(LFA): flow assay.

(CFU mL^{-1}): colony forming unit.

LOD: sensitivity/limit of detect.

(SPIONs): superparamagnetic iron oxide NPs.

(T2MR): T2 magnetic resonance.

(SERS): A surface-enhanced Raman scattering.

(MDR): multidrug resistance.

(LC-MS-MS): Liquid Chromatography with tandem mass spectrometry.

(SPR) peak: surface Plasmon resonance (SPR) peak at ~450 nm.

(ROS): reactive oxygen species.

(MALDI-MS): matrix-assisted laser desorption–ionization.

(Gd-DTPA): gadolinium-diethylenediamine penta-acetic acid.

(sTREM-1): soluble triggering receptor expressed on myeloid cells-1.

(PBPs): Penicillin binding proteins.

(LPS): Lipopolysaccharide.

(FcMBL): Fc-mannose-binding lectin.

(AMPs): Antimicrobial peptides.

(EVs): Extracellular vesicles.

(PAMPs): Pathogen-associated molecular patterns.

(TLRs): The Toll-like receptors recognize pathogen-associated molecular patterns (PAMPs) to activate immunity and inflammatory cascades.

(GM-CSF): Granulocyte-macrophage colony-stimulating factor.

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Table 1. Nanotechnology-based approaches for sepsis diagnosis and monitoring

Technique	Used nanoparticle	Aim and role	Ref.
Colorimetric bio sensing (surface-enhanced Plasmon resonance effect)	AuNPs	Naked eye detection of pathogens and metabolic activity assessment of pathogens	[29-32,35-38,72]
Lens-free interferometric microscopy (LIM)	Au nanohole substrates	Enhancement of optical signals	[39, 40]

Technique	Used nanoparticle	Aim and role	Ref.
Fluorescence resonance energy transfer (FRET)	Silica NPs, QDs	Fluorescent signal amplification	[48-52]
Magnetic resonance imaging (MRI)	Magnetic NPs, SPIONs	Contrast agents	[55-59,61, 64,74]
Surface-enhanced Raman scattering (SERS)	Au-coated MNPs, Magnetic core–polymeric shell biomimetic NPs	Sepsis biomarkers capturing	[62, 63]
Mass spectrometry MS)	MNPs, Liposomes	Mass spectrum enrichment	[65, 70]
Polymerase chain reaction (PCR)	SPIONs, AuNPs, MNPs	DNA amplification	[30-32,34-36,55-57,59, 60]

Table 2. Comparison of Nano diagnostic technologies for sepsis

Used nanoparticle	Size [nm]	Target molecules	Sample	Process time	Technique	Sensitivity/Limit of Detection (LOD)	Ref.
Mercaptoalkyloligonucleotide-conjugated AuNPs	13	DNA	Salmon sperm DNA	–	Colorimetric-based PCR	10 fmol	[31]
DNA-modified AuNPs	50	*mecA* gene of *S. aureus*	Genomic DNA from cultured bacterial cells	2 h	Colorimetric-based PCR	333 zmol or 2×10^5 molecules	[32]
Oligonucleotide-functionalized AuNPs and MMPs	13	Proteins and DNA	Buffers, human cerebral spinal fluid and serum	9–10 h	PCR	Proteins: 10^{-18} MDNA: 10^{-19} M	[34]
Silver-enhanced AuNPs Verigene	13–20	Gram-positive bacteria and DNA	Blood culture	2.5 h	PCR	$\approx 10^5$ CFU mL^{-1}	[35]
Nucleotide-labelled AuNPs and vancomycin-conjugated magnetic beads	20	*E. coli, K. pneumonia, P. aeruginosa*, and *S. aureus*	Cultured bacterial cells	25 min	Colorimetric-based integrated microflui	10^2 CFU mL^{-1}	[36]

Used nanoparticle	Size [nm]	Target molecules	Sample	Process time	Technique	Sensitivity/Limit of Detection (LOD)	Ref.
					dic device		
AuNPs	100	*P. mirabilis*	Human urine	40 min	Colorimetric	10 CFU mL^{-1}	[37]
AuNPs	45–50	IL-6	IL-6 buffer solution and IL-6 spiked blood	17 min	Colorimetric-based mobile biosensor	Buffer: 0.1 pg mL^{-1} Blood: 12.5 pg mL^{-1}	[38]
Au nano hole substrate	200	*E. coli*	Human plasma	40 min	Interferometric microscopy	400 CFU mL^{-1}	[39]
Au nano hole substrate	200	CRP, IL-6, and miRNA-16	Protein- and miRNA-spiked PBS	–	Interferometric microscopy	CRP: 18 µg mL^{-1} IL-6: 88 µg mL^{-1} miRNA-16: 6 µg mL^{-1}	[40]
Oligonucleotide-Au NP-conjugated PS nanobreaks	200	*S. aureus*	DNA	100 min	Diffusometric sensing	10×10^{-12} M	[41]
Mannose carbon QDs	3	*E. coli* K12 strain	Cell culture and human urine	1 h	Fluorescence	Cell culture: 450 CFU mL^{-1} Human urine: 10^3CFU mL^{-1} in	[48]
CdSe-QDs	8	CRP and IL-6	CRP and IL-6 spiked PBS (10% serum)	30 min	Fluorescence-based LFA	CRP: 42.5×10^{-9} M IL-6: 0.21×10^{-12}M	[49]
Silica NPs	60	*E. coli*O157:H7 cells	Cultured bacterial cells	20 min	Fluorescence	1 bacterium/100 µL sample	[50]
Silica NPs	60	*E. coli*, *S. aureus*, and *S. typhimurium*	Cultured bacterial cells	30 min	Fluorescence	–	[51]

Used nanoparticle	Size [nm]	Target molecules	Sample	Process time	Technique	Sensitivity/Limit of Detection (LOD)	Ref.
Silica MNPs and fluorophore-loaded silica NPs	187	*MNase of S. aureus*	Whole blood	10 min	Fluorescence	682 cells mL^{-1}	[52]
SPIONs	800	5 *Candida* species	Whole blood	3–5 h	PCR	1–3 CFU mL^{-1}	[55,56]
MNPs	<10	*S. aureus*	Cultured bacteria spiked media	1 h	Microfluidic chip-based μHall device	≈10 cells/1 μL	[58]
MNPs	20	16S rRNA of 13 bacterial species	Cells and whole blood	2 h	PCR and micro nuclear MRI	DNA:0.5×10^{-12}M or1–2 bacteria/10 mL of blood	[59,61]
Au-coated MNPs	20	CRP, PCT, and sTREM-1 proteins	Human serum	–	SERS-based immunoassay	CRP: 27 × 10^{-12} M PCT: 103 × 10^{-12}M sTREM-1: 78 × 10^{-12} M	[62]
Magnetic core–polymeric shell biomimetic NPs	1000	*S. aureus*	Bacterial cell culture	–	SERS	10 CFU mL^{-1}	[63]
HA-coated DTPA-Gd SPIONs	12	ROS	LPS-induced sepsis mice	20 min	MRI	0.2 × 10^{-6} M	[64]
(3-Aminopropyl) triethoxysilane modified MNPs	<15	PBPs from *S. aureus* and *E. coli*	Bacterial cell culture	–	MALDI-MS	10^{3}–10^{4} CFU mL^{-1}	[65]
AmBisome Liposomes	100	Unknown protein biomarkers	Human plasma	–	LC-MS/MS	–	[70]

Table 3. Summary of benefits, concerns, and current phase of clinical trials for novel therapeutics for sepsis.

Therapy	Benefit	Concern	Phase of Clinical Trial
PAMP Removal	Improved hemodynamics; improved mortality in murine model	Differing mechanisms/targets of removal between devices. No studies assessing effect on	Emergency Food and Drug Administration (FDA)-approval for Covid-19, ongoing

Therapy	Benefit	Concern	Phase of Clinical Trial
		mortality to date	multicentre clinical trials [79]
Bacteriophages	Can neutralize multidrug-resistant (MDR) bacteria	No randomized controlled data assessing efficacy	Case reports in humans [80]
Intravenous immunoglobulin (IVIG)	Useful in certain inflammatory conditions	No defined benefit in sepsis patients	FDA-approved for immunodeficiency's and inflammatory conditions
Targeted Monoclonal Antibodies	Avoids antibiotics resistance	Each drug only effective against targeted organism	Phase 3 trials underway [81]
Liposomes	Can bind bacterial toxin to minimize damage	Limited use in bacteria that secrete endotoxin	Phase 1 trials completed [82]
Alkaline Phosphatase	Mortality reduction in septic shock with acute kidney injury	Benefit found in only those with acute kidney injury	Phase 2 trials [83]
Antimicrobial Peptides	Synergism with antimicrobials	Cytotoxicity towards host cells	Phase 3 trials [84]
Nanoparticles	Increase potency and minimize side effects of antimicrobials	High development costs	Liposomal amphotericin B FDA-approved [85]
Angiotensin II	Catecholamine-sparing effect; improved mortality in certain patient populations	Limited prospective experience outside of phase III trials	FDA-approved for use in septic shock
Selepressin	Catecholamine-sparing effect with lower net fluid balance	No change in ventilator/vasopressor-free days	Phase 3 trial completed [86]
Mesenchymal Stem Cells	Decreased cell injury in murine sepsis models	Concern for oncogenicity	Phase 2 trials [81]
Extracellular Vesicles	Shown to improve renal recovery in murine models of sepsis	No standard nomenclature/isolation techniques	Phase 2 trials [87]
TLR4 Ligand Binders	Positive results in murine models of sepsis	Potentially oncogenic	FDA-approved only in the setting of cancer therapy
Interleukin agonists/antagonists	IL-7 agonist: prevents lymphopenia in septic shock; Anakinra: improved mortality in those with elevated IL-1RA levels;	IL-7 agonist: No mortality benefit in current trials; Anakinra: No data for routine use in sepsis IL-6R and IL-6 antagonist: mixed	Phase 2 trials [88]; Anakinra FDA-approved for rheumatoid arthritis IL-6R and IL-6 antagonist: phase 2 and phase 3 trials [89]; FDA-approved for rheumatoid

Therapy	Benefit	Concern	Phase of Clinical Trial
	IL-6R and IL-6 antagonist: attenuates cytokine storm	data, no data for non-covid sepsis	arthritis, EUA for Covid-19
cGAS-STING (cyclic GMP-AMP synthase-stimulator of interferon genes)	Murine models of sepsis demonstrated survival benefit	No in human data to suggest benefit in sepsis	FDA-approved for non-small lung cancer
Adrenomedullin	Potentialto decrease capillary permeability in sepsis	Concern with potential of hypotension	Phase 2 trials [81]
Eculizumab	Improved multiorgan dysfunction in Baboon models of sepsis	May lead to immunosuppression	FDA-approved for use in atypical haemolytic uremic syndrome
Interferon Gamma	Case series demonstrating improved cytokine profile	No RCT studying IFN-ɣ in sepsis	FDA-approved for chronic granulomatous disease and certain malignancies
Soluble TREM-1 and Nangibotide	Improved SOFA scores, especially in those with elevated sTREM-1 levels	Short half-life requires infusion	Phase 2 trials [90]
Immune Checkpoint Modulators	Improved absolute lymphocyte count (ALC) in those with low ALC and septic shock	Patient relevant clinical outcomes unknown	Phase 2 trials [88]
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Reduced length of mechanical ventilation for sepsis-induced immunosuppression	No clear mortality benefit in sepsis	FDA-approved for chemotherapy-induced neutropenia