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Review Article

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Nanotechnology in Sepsis: A Systematic Review of Diagnostic and Therapeutic Advancements

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ABSTRACT

Introduction: Sepsis is a global health emergency marked by a dysregulated host response to infection, leading to life-threatening organ dysfunction. Timely diagnosis and effective treatment are critical but remain challenging due to the limitations of conventional diagnostics, such as blood cultures and standard biomarkers (CRP, PCT), which often lack sensitivity, specificity, and rapid turnaround.

Objective/Aim: To systematically review recent advancements in nanotechnology-based diagnostics and therapeutics for the improved management of sepsis.

Methods: A comprehensive analysis of peer-reviewed literature was conducted, focusing on the application of various nanomaterials and nanotechnologies in sepsis diagnostics and therapy. Key technologies included magnetic nanoparticles, gold nanoparticles, quantum dots, carbon nanotubes, and hybrid nanoplatforms.

Results: Nanomaterials have demonstrated high potential in enhancing sepsis diagnostics through ultra-sensitive, specific, and real-time biosensing of host and microbial biomarkers. These platforms support multiplexed and point-of-care detection. In therapeutics, nanoparticle-based drug delivery systems and biomimetic carriers have improved targeted delivery, pharmacokinetics, and immune modulation. These innovations are particularly significant in the context of rising antimicrobial resistance.

Conclusion: Nanotechnology offers transformative potential in sepsis care by enabling early diagnosis and personalized treatment. However, challenges related to regulatory approval, safety, scalability, and clinical translation must be addressed. Integrating these technologies into standard care pathways could significantly improve outcomes in diverse healthcare settings.

Keywords: Sepsis, Nanotechnology, Nanodiagnostics, Nanotherapeutics, Biosensors, Antimicrobial Resistance, Point-of-care testing, Targeted Drug Delivery

INTRODUCTION

Sepsis remains a leading cause of global morbidity and mortality, affecting approximately 49 million individuals annually and resulting in 11 million deaths worldwide.[1] It arises from a dysregulated host response to infection, often leading to life-threatening organ dysfunction. Early and accurate diagnosis is essential for effective treatment, yet traditional diagnostic techniques, such as blood cultures, suffer from long turnaround times and limited sensitivity.[2]

Advancements in nanotechnology have introduced promising avenues for the rapid and sensitive detection of sepsis-related biomarkers and pathogens. Nanomaterials such as gold nanoparticles, quantum dots, carbon nanotubes (CNTs), and magnetic nanoparticles (MNPs) are increasingly employed in biosensing platforms due to their high surface-to-volume ratio, unique optical and electrical properties, and ability to be functionalized with biomolecules.[3] These nanotechnologies enable point-of-care testing that can significantly reduce diagnostic delays, critical in improving clinical outcomes.

Recent innovations include quantum dot-based multiplex assays for simultaneous detection of multiple sepsis biomarkers, CNT-based electrochemical sensors for procalcitonin and interleukin-6, and MNP-assisted immunoassays for rapid bacterial identification.[4] Moreover, peptide-functionalized nanoplatforms have shown increasing utility, leveraging high selectivity and biocompatibility for targeted detection and drug delivery in septic patients.[5]

Despite these emerging technologies, a comprehensive and up-to-date systematic evaluation of nanomaterials covering both diagnostic and therapeutic approaches in sepsis remains scarce. This review addresses that void by exploring the landscape of nanotechnology-based solutions developed

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in the past decade for sepsis diagnosis and management. By analysing the sensitivity, specificity, clinical potential, and limitations of these approaches, the review aims to inform future research and clinical translation.

METHODOLOGY

Study Design and Objective

This systematic review was conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** guidelines (Figure 1). However, the protocol was not prospectively registered due to the exploratory nature of the review and time constraints during its initiation. Despite this, all methodological steps were transparently reported and rigorously followed. The primary objective was to evaluate and synthesize recent advancements in nanotechnology-based diagnostic and therapeutic strategies for the management of sepsis. The study aimed to identify key trends, nanomaterial platforms, and outcome parameters in both preclinical and clinical research settings.

Figure 1: This illustrates the systematic review process, including the identification, screening, eligibility, and inclusion of studies.

Eligibility Criteria

Studies were included if they met the following criteria: (1) original research articles, reviews, or clinical reports focusing on nanotechnology-based approaches for sepsis diagnosis or treatment; (2) published in English; (3) published between January 2010 and June 2024; and (4) included *in vitro, in vivo*, or clinical evaluations of diagnostic sensitivity/specificity or therapeutic efficacy of nanomaterials. Exclusion criteria comprised studies not primarily focused on sepsis, articles lacking relevant outcome data, and non-peer-reviewed content such as opinion pieces, editorials, or commentaries.

Information Sources and Search Strategy

A comprehensive literature search was performed using four electronic databases: **PubMed, Scopus, Web of Science,** and **Google Scholar**. Search terms included both free-text keywords and Medical Subject Headings (MeSH), structured using Boolean operators (AND, OR) to capture relevant literature. The key search combinations included:

- "Sepsis" AND "Nanotechnology"
- "Nanoparticles" AND "Sepsis diagnosis"
- "Nanomedicine" AND "Antimicrobial resistance"
- "Nanoparticle drug delivery" AND "Sepsis treatment"
- "Point-of-care" AND "Sepsis biosensor"

The final search was conducted in **June 2024**. All citations were imported into **Zotero** for management, and duplicates were removed before screening.

Study Selection

Two reviewers independently screened all titles and abstracts for relevance. Full-text articles of potentially eligible studies were subsequently assessed. Any disagreements regarding inclusion were resolved by discussion or, when necessary, through consultation with a third reviewer. The selection process adhered to PRISMA flow diagram principles.

Data Extraction

Data extraction was carried out using a pre-designed and piloted form. Microsoft Excel was used to organize, categorize, and thematically analyze the included studies. NVivo or other software was not used in this review. Extracted data included (Table 1):

- Publication details (author, year, journal)
- Study design and model (*in vitro*, animal, clinical)
- Type of nanomaterial (e.g., gold nanoparticles [AuNPs], magnetic nanoparticles [MNPs], quantum dots [QDs], carbon nanotubes [CNTs])
- Diagnostic applications (e.g., biomarker detection, pathogen identification)
- Therapeutic applications (e.g., drug delivery, immune modulation)
- Key outcomes: sensitivity, specificity, detection limit, therapeutic efficacy, and survival benefit

RESULTS

Data Synthesis

Given the diversity of study designs, nanomaterial types, and reported outcomes, a **qualitative narrative synthesis** was employed. Findings were thematically organized into two principal categories:

1. **Nanotechnology in Sepsis Diagnosis**, and
2. **Nanotechnology in Sepsis Treatment**.

Within each domain, subthemes such as **point-of-care (POC) diagnostic platforms**, **multiplexed biosensors**, **nanoparticle-mediated drug delivery**, **biomimetic systems**, and **theranostic approaches** were analyzed. Trends and emerging innovations were highlighted and critically examined (Figure 2).

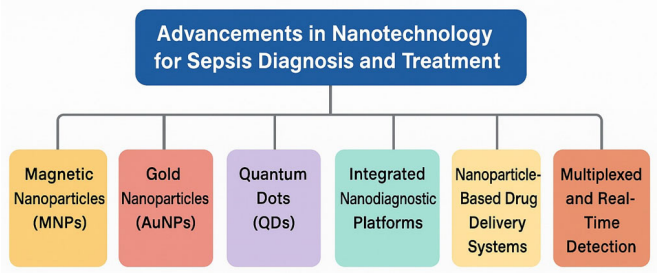

Figure 2: Overview of nanotechnology-based advancements in sepsis diagnosis and treatment. The diagram highlights key innovations, including nanoparticle-based drug delivery systems, integrated nanodiagnostic platforms, biomimetic nanoparticles, antimicrobial peptide carriers, point-of-care (POC) systems, multiplexed detection approaches, and theranostic nanoplatforms that collectively contribute to improved sensitivity, specificity, and therapeutic outcomes in sepsis management.

Nanotechnology in Sepsis Diagnosis and Treatment

Nanotechnology in Sepsis Diagnosis

Nanotechnology-enabled diagnostic tools, collectively known as nanodiagnostics, utilize engineered nanomaterials to achieve high sensitivity, specificity, and speed in detecting sepsis-related pathogens and biomarkers. These systems overcome the limitations of traditional diagnostics by enabling real-time detection and integration into point-of-care (POC) platforms.[1] Key materials include magnetic nanoparticles (MNPs), gold nanoparticles (AuNPs), quantum dots (QDs), and other nanosensors, which offer unique physicochemical properties beneficial for biosensing. Nanodiagnostics are particularly useful for their high sensitivity, specificity, and ability to detect pathogens and biomarkers in real-time (Table 1).[2]

1. Magnetic Nanoparticles (MNPs)

Magnetic nanoparticles (MNPs) are widely used in biomedical diagnostics due to their superparamagnetic properties, which facilitate rapid separation and enrichment of pathogens from complex biological fluids. Functionalization of MNPs with biomolecules such as antibodies or oligonucleotides enables the selective capture of sepsis-related pathogens or biomarkers. Researchers have demonstrated that vancomycin-conjugated polydopamine-coated MNPs effectively captured a wide range of Gram-positive bacteria from blood samples. The approach enhanced diagnostic sensitivity and reduced sample processing time, achieving a detection limit as low as 10 CFU/mL.[3] In another study, a microfluidic biosensor integrating MNPs for magnetic separation, quantum dots (QDs) for fluorescent labeling, and MnO_2 nanoflowers for signal amplification was developed for the detection of *Salmonella typhimurium*. This platform offered a wide detection range and a low detection limit, showcasing the potential of integrated nanodiagnostic systems in sepsis diagnosis.[4]

2. Gold Nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) have unique optical properties, particularly localized surface plasmon resonance (LSPR), which makes them ideal for colorimetric biosensing. These particles are frequently used in lateral flow assays for the detection of sepsis biomarkers. Taranova et al. (2017) developed a bifunctional AuNP-based lateral flow assay for detecting procalcitonin, a key sepsis biomarker.[5] The platform showed enhanced sensitivity and enabled visual detection with the naked eye within minutes. Similarly, Han et al. (2020) discussed the use of AuNPs in combination with liposomes and polymeric carriers to enhance both the detection and therapeutic delivery in sepsis, paving the way for multifunctional diagnostic platforms.[6] AuNPs have also been used to detect bacterial DNA via colorimetric shifts, enabling identification of pathogens within a few hours.[7] These technologies hold particular promise in resource-limited settings due to their simplicity and affordability.

3. Quantum Dots (QDs)

Quantum dots (QDs) are semiconductor nanocrystals with unique fluorescent properties, offering high brightness and photostability. These characteristics make them suitable for multiplexed detection of sepsis biomarkers. The development of peptide-functionalized QD nanosystems capable of detecting both protein and nucleic acid markers associated with sepsis has been reported.[8] In point-of-care applications, QDs have been employed to simultaneously detect C-reactive protein (CRP) and procalcitonin, achieving high sensitivity and specificity in lateral flow assays.[9,10] Moreover, integration of QDs with MNPs and microfluidics has enabled the development of platforms that not only enhance

detection sensitivity but also reduce assay times, making them attractive for emergency diagnostics.[11]

4. Integrated Nanodiagnostic Platforms

Recent trends in nanodiagnostics involve the integration of multiple nanoparticle systems to improve diagnostic efficiency. For instance, the combination of MNPs for target enrichment, QDs for signal transduction, and nanostructured materials like MnO_2 nanoflowers for amplification has led to platforms capable of detecting pathogens with high accuracy and low limits of detection.[8,12] These hybrid systems enable simultaneous detection of multiple biomarkers, real-time monitoring, and even therapeutic delivery, which is particularly useful in the complex pathophysiology of sepsis.[2,13]

5. Point-of-Care (POC) Diagnostic Platforms

Nanotechnology has enabled the development of miniaturized POC platforms that combine rapid diagnostics with ease of use, crucial in emergency or ICU settings. These platforms integrate nanomaterials with microfluidics or optical sensors to detect bacterial antigens or host biomarkers on-site. For instance, a dual-enhanced plasmonic biosensor integrated with chemifluorescence signal amplification detected IL-6 and TNF-α at sub-pg/mL levels within one hour from patient plasma samples.[14]

6. Multiplexed and Real-Time Detection Approaches

Sepsis often involves complex pathophysiology, requiring simultaneous detection of multiple biomarkers and pathogens. Nanotechnology enables the integration of multiplexed biosensors that can detect multiple targets in real-time. A plasmon-enhanced fluorescence detection system developed by Zhang et al. enabled the simultaneous quantification of 5 inflammatory cytokines with high sensitivity and 100% clinical accuracy. [18]

Table 1: Summary of Nano-Diagnostic Platforms

Nanomaterial	Biomarker/Target	Sensitivity	Specificity	Advantage
Gold nanoparticles (AuNPs)	Procalcitonin (PCT), cytokines	Low pg/mL	High with functionalization	Fast, scalable, label-free detection
Peptide-coated liposomes	Bacterial membrane proteins	High specificity at nanomolar	Selective via peptide recognition	Biocompatibility, dual role in therapy
Quantum dots (QDs)	Interleukin-6 (IL-6), TNF-α	Femtomolar range	Excellent due to multiplexing	Bright fluorescence, long-term tracking
Magnetic nanoparticles (SPIONs)	Lipopolysaccharides (LPS)	Low ng/mL	Moderate to high	Magnetic enrichment, real-time sensing
Metal–organic frameworks (MOFs)	Reactive oxygen species (ROS), bacterial toxins	Broad dynamic range	Target-responsive specificity	Stimuli-responsive diagnostics

Nanotechnology in Sepsis Treatment

Despite medical advancements, sepsis treatment remains a challenge due to the heterogeneous nature of the disease, multidrug resistance (MDR), and the limitations of conventional therapies. Nanotechnology has emerged as a transformative tool in enhancing the efficacy of sepsis treatments by enabling precise drug delivery, improving bioavailability, modulating immune responses, and facilitating co-delivery of synergistic agents (Table 2).[2,15]

1. Nanoparticle-Based Drug Delivery Systems

Nanoparticles offer a versatile platform for encapsulating therapeutic agents and directing them to infection sites. By improving drug solubility, stability, and bio-distribution, nanoparticle carriers can reduce off-target effects and enhance therapeutic efficacy.

a. Polymeric Nanoparticles

Polymeric nanoparticles such as poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan are widely used for their biocompatibility and controlled release properties. For instance, encapsulated anti-inflammatory drugs like atorvastatin in PEGylated PLGA nanoparticles to treat sepsis-induced acute kidney injury. The nanoparticles provided sustained release and enhanced renal accumulation, leading to significant improvement in renal biomarkers and histopathology.[16] Another study utilized chitosan-coated PLGA nanoparticles to deliver rifampicin, an antibiotic, directly to infected macrophages. The targeted approach increased intracellular drug concentration and bacterial clearance.[17]

b. Lipid-Based Nanoparticles

Lipid-based nanocarriers, including liposomes and solid lipid nanoparticles (SLNs), have shown promise in improving the pharmacokinetics of antibiotics and anti-inflammatory agents. Mannosylated liposomes loaded with ciprofloxacin demonstrated enhanced targeting of alveolar macrophages in pulmonary infections, improving local antibacterial efficacy and reducing systemic toxicity.[18]

2. Antimicrobial Peptides (AMPs) in Nanocarriers

AMPs are host-derived peptides with potent antibacterial and immunomodulatory activity. However, their clinical application is limited by enzymatic degradation and cytotoxicity. Nanocarriers offer protection and facilitate controlled release at the infection site. Clavanin A, a marine-derived AMP, was encapsulated in polymeric nanoparticles and tested in a murine sepsis model. The encapsulated AMP maintained its bioactivity, reduced bacterial burden, and significantly, improved survival compared to free peptide administration.[19] In an innovative strategy, mRNA encoding AMPs and lysosomal enzymes was delivered via lipid nanoparticles. The nanoparticles transfected macrophages, enhancing their bactericidal activity through intracellular AMP expression, leading to increased survival in septic animals.[15]

3. Co-Delivery Systems for Synergistic Therapy

Nanoparticles can be engineered to co-deliver multiple agents, such as antibiotics, anti-inflammatory drugs, and antioxidants, for a synergistic therapeutic effect. Luo et al. developed lipid nanoparticles to co-deliver the NLRP3 inflammasome inhibitors MCC950 and disulfiram. These agents synergistically reduced IL-1β and IL-18 production in macrophages and improved survival in polymicrobial sepsis models.[20] Another platform employed mesoporous silica nanoparticles loaded with nitric oxide donors and gentamicin. This design disrupted bacterial biofilms, an important feature in chronic infections, while simultaneously delivering antibiotics, reducing the biofilm viability by more than 90%.[21]

4. Biomimetic Nanoparticles for Immune Modulation

An excessive and uncontrolled immune response is a hallmark of sepsis. Biomimetic nanoparticles, such as cell-membrane-coated systems, can sequester cytokines, neutralize endotoxins, and restore immune balance. Thamphiwatana et al. designed macrophage-mimicking nanoparticles by coating polymeric cores with macrophage membranes. These particles absorbed circulating endotoxins (e.g., lipopolysaccharides) and pro-inflammatory cytokines (e.g., TNF-α, IL-6), reducing systemic inflammation and organ damage in septic mice.[22] Similarly; red blood cell membrane-coated nanosponges have been engineered to neutralize bacterial toxins, effectively reducing septic shock in animal models. These nanosponges act as decoys, preventing host cell lysis and modulating the immune response.[23,24]

5. Theranostic Nanoplatforms

Emerging research focuses on integrating diagnostic and therapeutic functionalities, so-called theranostic nanoplatforms. These systems enable simultaneous pathogen detection and real-time therapeutic intervention. Koide et al. developed hydrogel-based nanoparticles that respond to the inflammatory environment by releasing encapsulated drugs while simultaneously emitting fluorescent signals to track infection sites.[15] This dual-function system allows real-time monitoring of therapeutic response, improving treatment precision and clinical decision-making.

Table 2: Nanotechnology-based Therapeutic Platforms

Strategy	Nanocarrier Type	Payload / Agent	Mechanism of Action	Model / Outcome
1. Polymeric Nanoparticles	PEGylated PLGA	Atorvastatin	Sustained release; enhanced renal targeting	Improved renal biomarkers in sepsis-induced AKI model[16]
	Chitosan-coated PLGA	Rifampicin	Targeted delivery to infected macrophages; enhanced intracellular antibiotic concentration	Increased bacterial clearance[17]
2. Lipid-Based Nanoparticles	Mannosylated liposomes	Ciprofloxacin	Targeting alveolar macrophages; improved local drug accumulation	Enhanced antibacterial efficacy; reduced systemic toxicity[18]
3. AMPs in Nanocarriers	Polymeric nanoparticles	Clavanin A (marine AMP)	Protection from degradation; sustained release	Improved survival in murine sepsis model[19]
	Lipid nanoparticles	mRNA encoding AMP & lysosomal enzymes	Transfection of macrophages; enhanced intracellular AMP expression	Boosted macrophage bactericidal activity; higher survival[15]
4. Co-Delivery Systems	Lipid nanoparticles	MCC950 + Disulfiram	NLRP3 inflammasome inhibition; synergistic cytokine suppression	Improved survival in polymicrobial sepsis[20]
	Mesoporous silica nanoparticles	Nitric oxide donor + Gentamicin	Biofilm disruption + antibiotic delivery	>90% reduction in biofilm viability[21]

Table 2: ***(Continued)***

Strategy	Nanocarrier Type	Payload / Agent	Mechanism of Action	Model / Outcome
5. Biomimetic Nanoparticles	Macrophage membrane-coated polymeric core	Endotoxin & cytokine absorption	Immune modulation via toxin/cytokine sequestration	Reduced systemic inflammation & organ damage[22]
	RBC membrane-coated nanosponges	Broad-spectrum bacterial toxins	Act as toxin decoys; prevent host cell lysis	Lower septic shock incidence in animal model[23,24]
6. Theranostic Nanoplatforms	Inflammation-responsive hydrogel nanoparticles	Fluorescent dyes + therapeutic drugs	Simultaneous inflammation-triggered drug release and pathogen localization via fluorescence	Real-time treatment monitoring & site-specific therapy[15]

Future Directions and Challenges

Nanotechnology has shown immense promise in revolutionizing the diagnosis and treatment of sepsis through enhanced sensitivity, targeted drug delivery, and real-time monitoring capabilities. However, despite encouraging laboratory and preclinical results, several critical challenges must be addressed before nanotechnology-based solutions can be widely implemented in clinical settings.

One of the foremost challenges lies in the scalability of nanoparticle manufacturing. While many nanosystems demonstrate efficacy in controlled environments, reproducing these materials consistently at a commercial scale, with uniform quality and functionality, remains complex and cost-intensive. Batch-to-batch variability and the requirement for sophisticated fabrication infrastructure limit the feasibility of large-scale production.

Biocompatibility and safety represent another major concern. Nanoparticles can interact unpredictably with biological systems, leading to potential toxicity, immunogenicity, or unintended biodistribution. Long-term safety data are often lacking, and the degradation products of some nanomaterials may pose additional health risks. To address these concerns, ongoing research must focus on developing biodegradable, non-toxic, and immune-stealth materials that can be safely metabolized or excreted by the body.

Regulatory challenges also hinder the clinical translation of nanotechnologies. The complex nature of nanoscale formulations makes it difficult to evaluate them using conventional regulatory frameworks designed for small-molecule drugs or biologics. Regulatory agencies, such as the FDA and EMA, require comprehensive preclinical studies, standardized characterization protocols, and extensive clinical trial data to ensure safety and efficacy. The absence of harmonized international standards further complicates the approval process and delays market entry.

Moreover, the economic viability and cost-effectiveness of nano-based sepsis interventions must be carefully evaluated. Advanced nanomedicine approaches may incur higher development and production costs, which can pose challenges for adoption in resource-limited healthcare systems. Future research must address these concerns by designing cost-efficient, easily integrable platforms compatible with existing diagnostic and therapeutic workflows.

Looking ahead, future directions should include refining nanoparticle properties, such as size, surface chemistry, and targeting ligands, to maximize diagnostic sensitivity and therapeutic precision. Multifunctional nanoplatforms capable of simultaneous detection, drug delivery, and monitoring (theranostics) represent a particularly promising avenue. Additionally, integrating nanotechnology with artificial intelligence and microfluidics could pave the way for smart, point-of-care diagnostic systems that enable rapid, personalized treatment decisions in critical care settings.

In summary, while the potential of nanotechnology in sepsis management is considerable, overcoming the technical, regulatory, and economic barriers will be essential to realizing its full clinical impact. Interdisciplinary collaboration among material scientists, clinicians, regulatory experts, and industry stakeholders will be key to accelerating progress in this evolving field.

CONCLUSION

Nanotechnology offers transformative potential in the early diagnosis and personalized treatment of sepsis. The integration of nanotechnology into clinical practice could significantly reduce the time to diagnosis and improve the management of sepsis, particularly in the face of increasing antimicrobial resistance. Further research and development are needed to address the current challenges and bring these technologies to the clinic, ultimately improving outcomes for patients with sepsis. Critical steps toward clinical translation include pilot human trials, GMP-grade nanoparticle synthesis, AI-driven data integration for decision support, and strategies to ensure global accessibility and equity in resource-limited settings.

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Authors' Contribution:

P.B. conceptualized and designed the study. N.V.M. and S.S. conducted the literature search and data extraction. P.B., N.V.M., and S.S. performed the data analysis and created visualizations. N.V. M. drafted the manuscript. All authors critically reviewed the manuscript, contributed to revisions, and approved the final version.

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