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REVIEW

The Potential of Drug Delivery Nanosystems for Sepsis Treatment

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Abstract: Sepsis is a major immune response disorder caused by infection, with very high incidence and mortality rates. In the clinic, sepsis and its complications are mainly controlled and treated with antibiotics, anti-inflammatory, and antioxidant drugs. However, these treatments have some shortcomings, such as rapid metabolism and severe side effects. The emergence of drug delivery nanosystems can significantly improve tissue permeability, prolong drugs' circulation time, and reduce side effects. In this paper, we reviewed recent drug delivery nanosystems designed for sepsis treatment based on their mechanisms (anti-bacterial, anti-inflammatory, and antioxidant). Although great progress has been made recently, clinical practice transformation is still very difficult. Therefore, we also discussed key obstacles, including tissue distribution, overcoming bacterial resistance, and single treatment modes. Finally, a rigorous optimization of drug delivery nanosystems is expected to present great potential for sepsis therapy.

Keywords: sepsis, anti-bacterial, anti-inflammatory, anti-oxidative, drug delivery nanosystems, multidrug resistance

Introduction

Sepsis, a life-threatening organ dysfunction caused by the host immune response to infection, is one of the leading causes of death worldwide. According to a recently published study,[1] 48.9 million sepsis cases and 11 million sepsis-related deaths were recorded in the world in 2017, accounting for about 20% of global deaths.[2] Among them, septic shock and multiple organ dysfunction mortality can be as high as 50%. Although critically ill sepsis patients' management has improved in the past decade, sepsis-related mortality is still high.[3,4] The global age-standardized sepsis incidence rate dropped from 1074.7 cases per 100,000 in 1990 to 67.5 cases per 100,000 in 2017, showing a decrease of 37.0%. The percentage of global deaths related to age-standardized sepsis dropped from 29.1% in 1990 to 20.1% in 2017, indicating a decrease of 31.0%.[5] Moreover, the prognosis of sepsis is severe. A total of 30% of survivors can develop long-term dysfunction and cognitive impairment,[6] leading to a tremendous burden to society and individuals.

Sepsis management guidelines focus on three main components:[7] (1) hemodynamic stability, (2) infection control, and (3) sepsis response regulation. Other interventions include organ support non-specific measures, such as oxygen therapy, mechanical ventilation, hemodynamic support, corticosteroids, and renal replacement therapy.[8] Often, sepsis management is based on multimodal treatment severity. For example, mild single organ dysfunction can be controlled by appropriate support, while multiple organ dysfunction requires invasive treatments.

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Antibiotic treatments are the standard in clinical guidelines for sepsis. However, 70–80% of sepsis deaths are related to persistent infection, indicating widespread antibiotic resistance and a lack of effective antibiotics. For example, it is estimated that 214,000 neonatal septicemia deaths are caused by drug-resistant pathogens worldwide.[9,10] In neonatal drug resistance, *Escherichia coli* showed resistance to β-lactam antibiotics and aminoglycosides; group *B streptococci* were resistant to penicillin; *Listeria monocytogenes* were resistant to cephalosporins and vancomycin; *Staphylococcus aureus* and *coagulase-negative staphylococci* were not sensitive to vancomycin and methicillin.[11,12] This drug resistance can harm sepsis prognosis and almost double mortality.

Additionally, although antibiotics' timely administration is very active, the host sepsis response can trigger the systemic release of various cytokines, reactive oxygen species, and other biomolecules. This can be overwhelming and easily lead to multiple organ failures and death. Recent clinical data showed that despite more than 60% of sepsis patients surviving the initial inflammatory storm, they rapidly developed a longer immunosuppressive state, characterized by paralysis and immune cells' death, resulting in the inability to remove invasive pathogens increasing hospital-acquired infection susceptibility, and high mortality. Therefore, new adjuvant therapies such as anti-inflammatory agents, immunomodulators, and antioxidants are being explored. However, many anti-inflammatory agents and antioxidants are limited by a short half-life, lack of tissue or cell-specific targeting ability, and poor water solubility and bioavailability. Additionally, due to cellular enzymes activities, some peptides showed significant anti-inflammatory activity in vitro but could not reproduce this effect in vivo. Additionally, complex pathophysiology involving multi-channel cytokine storms requires a multi-pronged approach since single-drug approach may not be effective.

The emergence of nanotechnology has opened up a new pathway to overcome the serious adverse effects and resistance of drugs. Nanotechnology is a system that takes synthetic or natural materials as carriers and introduces drugs through various methods (grafting, adsorption, and physical encapsulation), which is called a drug-delivery nanosystem. Besides this, nanotechnology can also include nano-drug crystals that directly process raw drugs. This review only focuses on drug-delivery nanosystems. Most nanocarriers do not have any function (some special nanocarriers may show certain internal activities, such as photothermal performance, antioxidant performance, etc.), while drugs have nano-size and surface characteristics because they enter a new system, which significantly changes their own distribution and metabolic pathway to play a drug effect different from raw drugs. Different nanocarriers have been developed, including liposomes,[13,14] nanoparticles,[15] solid lipid nanoparticles,[16] polymer micelles,[17,18] and extracellular vesicles.[19–21] The employment of nanotechnology has great potential for accurate sepsis treatment, attributed to their proper physical and chemical properties (such as size, charge, surface chemistry, shape, etc.) and their possible surface functionalization. For example, a particle size ranging from 0.5 μm to 5 μm exerts an excellent pulmonary-targeting ability since the particles could be trapped by pulmonary capillaries.[22] Aiming at targeting renal tubule, drug-delivery nanosystems with a particle size smaller than endothelial fenestrations (70–90 nm) could be designed since nanocarriers need to pass anatomical barriers of endothelial fenestrations (70–90 nm) and be trapped in the gap between endothelial fenestrations and the glomerular basement membrane (2–8 nm). Furthermore, a positively charged drug-delivery nanosystem could be transported more easily than negatively charged drug carriers owing to the presence of negatively charged heparin sulfate and sulfated glycosaminoglycan on the fenestrae.[23,24] Additionally, drug-delivery nanosystems can also be engineered with peptides,[25] antibodies,[26] and oligonucleotides,[27] allowing site-specific delivery of drugs. These contribute to modulating the pharmacokinetics of the encapsulated drug, improving the efficacy, stability, and bioavailability.[28] All of these options together have prompted drug-delivery nanosystems for the precision treatment of sepsis.

Therefore, in this review, we introduced drug delivery nanosystems designed for sepsis treatment based on different mechanisms (eg, antibacterial, antioxidative, and anti-inflammatory). Meanwhile, we concluded and discussed the future outlooks of these systems.

Drug Delivery Nanosystems for Sepsis Treatments

Antibacterial Drug Delivery Nanosystems

Sepsis and its complications are mainly controlled and treated with antibiotics and other drugs. However, small-molecule drugs have disadvantages in the organism, such as a too-fast clearance rate, low utilization, high toxicity and side effects, which may lead to inappropriate treatment

effects. Recently, with material technology and nanotechnology's continuous development, studies involving antibacterial and anti-inflammatory drug delivery nanosystems, based on functional materials, have been published.[28–30] However, how to truly target the infection site and effectively treat and control sepsis has not been solved. Based on sepsis's pathological characteristics, Zhang et al[31] designed and developed bioresponsive nanoparticles for drug targeted delivery, achieving effective sepsis control and treatment. First, a pH/enzyme sensitive amphiphilic polymer was synthesized by Michael's step-by-step addition method, which could self-assemble into nano micelles and effectively load antibiotics and anti-inflammatory drugs. Then, through biotin-avidin specific action, targeted intercellular adhesion molecule-1 (ICAM-1) antibodies were modified on drug-loaded nano micelles' surface, and new drug delivery nanosystems with targeting effect were prepared. To evaluate biocompatibility, the cell viability of the prepared nanosystem was assessed in three cell lines (NHF, HUVEC, and HEK 293T). There was no obvious change in the percentages of survival cells after nanosystem treatment, implying nonsignificant cytotoxicity. In a sepsis mouse model caused by bacteria, the drug delivery nanosystems effectively eliminated the invasive bacteria and alleviated the inflammatory reaction, thus improving the survival rate. Altogether, these results confirmed the capability of the new drug delivery nanosystems for effective sepsis treatment.

Due to a serious increase in bacterial resistance, treating sepsis caused by drug-resistant bacteria infections is even more difficult. Macrophages, one of the main participants in host immune defense, mainly encapsulate bacteria in its phagocytic lysosomes, and kill bacteria through active nitrogen oxides and lysosomal enzymes activity. However, many bacteria, such as *Staphylococcus aureus* and *Escherichia coli*, can survive in cells, resisting bactericidal mechanisms and eventually leading to infection recurrence. Additionally, although antibiotic therapies are among the most basic treatments for bacterial sepsis, 70–80% of sepsis deaths are still accompanied by persistent infection, which might be due to a lack of effective antibiotics for some drug-resistant bacteria. To solve the drug-resistance problem, Hou et al[32] designed and constructed an mRNA encoding an antimicrobial peptide, an enzyme-sensitive linker peptide, and a lysosomal signal protein. They screened lipidic vitamins with optimal composition to prepare vitamin C nanoparticles. After the nanoparticles enter the macrophages, the mRNA is released into the cytoplasm, then translated into a triblock protein: antimicrobial peptide enzyme-sensitive peptide lysosomal signal protein. Under lysosomal signal protein guidance, the triblock protein enters the lysosome, and the sensitive enzyme peptide is cut off by lysosomal enzymes, and the antimicrobial peptide is finally released. When the macrophage contacted the bacteria, bacteria were first wrapped in the phagosome, and then the phagosome fused with the lysosome. At this time, the exogenous antimicrobial peptides and other bactericidal components in the lysosome dissolved into the phagosome, achieving a synergistic bactericidal effect, effectively reducing the number of drug-resistant bacteria in the body and improving the host's body function. Finally, the host's survival rate of sepsis induced by drug-resistant bacteria was improved. Surprisingly, the levels of bodyweight, white blood cells, and lymphocytes of the survived mice fully recovered after treatment, implying good biosafety.

The shape of nanoparticles is closely related to their biological distribution and interaction with target cells, affecting drug delivery characteristics. Anisotropic nanoparticles indicated that the shape of nanoparticles was not invariant with respect to direction. Compared with spherical nanoparticles, anisotropic ones have greater resistance to non-specific cell elimination when administered in the whole body, which would enhance the membrane-coated nanoparticles' stealth. Almost all previous bionic designs used spherical nanoparticles. To fabricate anisotropic nanoparticles, Ben Akiva et al[33] first synthesized spherical poly (lactic-co-glycolic acid) (PLGA) nanoparticles by single emulsion and then stretched them above the glass transition temperature of PLGA. Stretching two-fold in one dimension generated prolate nanoparticles, and 1.5-fold in two dimensions presented oblate ellipsoidal nanoparticles. After interaction with red blood cell membranes, three types of biomimetic anisotropic nanoparticles were yielded. The results showed that although the prepared anisotropic nanoparticles curvature radius increased, it did not significantly affect coating fluidity or stability, and can be covered by naturally derived cell membranes. Compared with uncoated spherical nanoparticles, anisotropic nanoparticles coated with red blood cell membrane can better escape macrophages' clearance and reduce 50 to 60% of internalization, resulting from the synergistic effect of altering the nanoparticle shape and introduction of the membrane. Moreover, the nanoparticles with a prolate ellipsoidal shape demonstrated a superior half-life (171.6 min) compared to any other nanoparticles (82.0 min for coated oblate ellipsoidal particles and 64.8 min for coated spherical particles). As a result,

approximately 50% of the mice treated with coated prolate ellipsoidal nanoparticles remained healthy 1 week after alpha toxin administration, whereas only 33% of the mice in the oblate ellipsoidal nanoparticles group showed one-week survival. Overall, anisotropic nanoparticles coated with red blood membranes are expected to be a potential treatment for improving the survival rate in patients with sepsis.

Moreover, the discovery of a new antibacterial nanomaterial is another important possibility for overcoming multi-drug resistance. Since S-thanatin (Ts) is an antibacterial peptide with specific targeting ability, it was modified onto the surface of the liposome to act both as the targeting moiety and antibacterial component[25] (Figure 1). Then, the antibiotic levofloxacin was loaded into liposomes with the ammonium sulfate gradient method. As displayed, Ts-anchored liposome significantly enhanced the bacterial internalization of the antibiotic, resulting in the synergistic effect of an antibiotic and antibacterial peptide. In mice receiving clinical multidrug-resistant (MDR) isolates, the bacterial was rapidly cleared by the fabricated drug delivery nanosystems, contributing to remarkably decreased lethality rate of the septic shock (100% in the control group within 36 h versus 93.3% in the Ts-modified drug delivery nanosystem within 72 h).

Graphene oxide (GO), a single layer with a two-dimensional honeycomb lattice structure by the carbon atoms, was regarded as a promising engineered nanoplatform due to the strong antibacterial effects. Many studies have explored the bacterial killing ability of GO-based drug delivery nanosystems with different physicochemical characteristics and their mechanisms of bacterial killing. For a summary of the antibacterial applications of GO-based drug delivery nanosystems, please refer to Zhang et al's review for details.[34]

Antioxidative Drug Delivery Nanosystems

Sepsis is an abnormal systemic inflammatory response mediated by excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) production. Excessive ROS and RNS can change a series of intracellular events and the function of different enzymes and ion channels. Therefore, reducing ROS and RNS levels in cells and mitochondria can inhibit sepsis's abnormal inflammatory response. Traditional organic antioxidants have low structural stability, poor ROS and RNS scavenging activity, and poor scavenging activity persistence under physiological conditions. Yim et al[35] prepared three kinds of 2D transition metal dichalcogenide nanosheets (Tungsten disulfide (WS_2), Molybdenum selenide ($MoSe_2$), and Tungsten diselenide (WSe_2)) by liquid phase-stripping using an amphiphilic copolymer (poly(ε-caprolactone)-b-poly(ethylene glycol)) (Figure 2). These exfoliated nanosheets displayed an average lateral size of 37.5 nm, thickness of 4 nm, and negative ζpotentials. The RNS and ROS scavenging experiment showed that the prepared WS_2, $MoSe_2$ and WSe_2 nanosheets could effectively remove mitochondrial and cytosolic ROS and RNS of inflammatory cells (including hydroxyl radicals, superoxide, hydrogen peroxide (H_2O_2), and nitric oxide). Compared with MoSe2 or WSe2 nanosheets, WS2 nanosheets can more effectively inhibit the excessive secretion of inflammatory cytokines except for the scavenging of ROS and RNS, contributing to significantly improved severe sepsis mice survival rate (up to 90%). Additionally, this pharmacokinetic study showed that WS2 nanosheets could be excreted in mice after intravenous injection for 3 days.

Ceria nanoparticles exhibit similar activities to superoxide dismutase (SOD) and catalase (CAT) through reversible

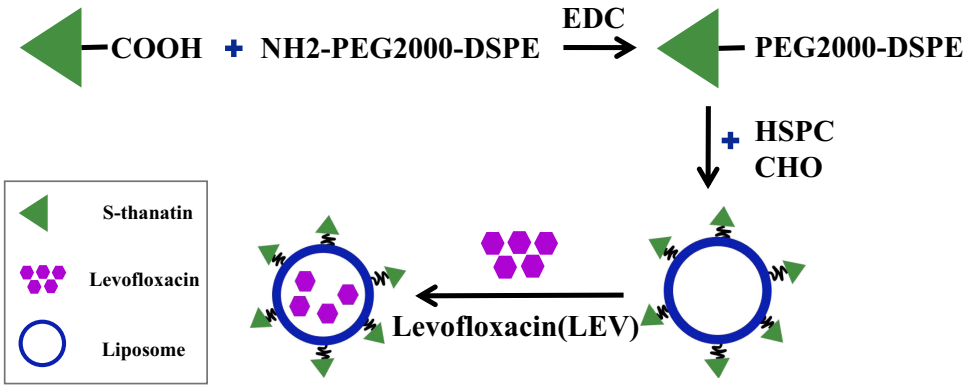

Figure 1 The preparation schema of S-thanatin-modifed liposomes loaded with levofloxacin. Reprinted with permission from Fan X, Fan J, Wang X, Wu P, Wu G. S-thanatin functionalized liposome potentially targeting on Klebsiella pneumoniae and its application in sepsis mouse model. *Front Pharmacol.* 2015;6:249.[25]

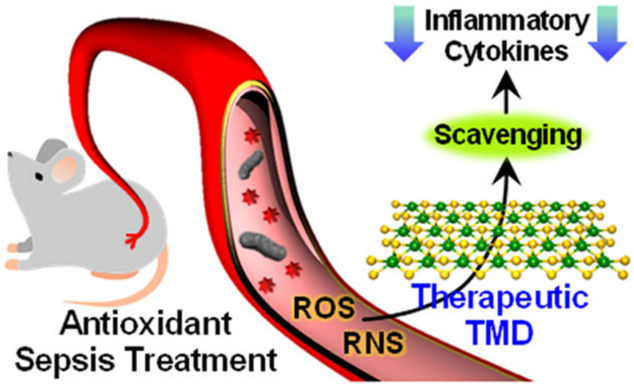

Figure 2 The treatment schema of 2D Transition Metal Dichalcogenide (TMD) Nanosheets. Reprinted with permission from Yim D, Lee DE, So Y, et al. Sustainable nanosheet antioxidants for sepsis therapy via scavenging intracellular reactive oxygen and nitrogen species. *ACS Nano*. 2020;14(8):10324–10336. Copyright (2020) American Chemical Society.[35]

conversion between Ce^{3+} and Ce^{4+} valence states and oxygen-binding.[36,37] They could eliminate H_2O_2, and superoxide anion (O_2-), and hydroxyl (●OH) radicals.[38,39] Compared with most small-molecule antioxidants, cerium oxide (CeO_2) nanoparticles have a stronger ROS scavenging ability and renewable activity, promising for antioxidant applications, and have been widely studied. Chen et al[40] synthesized polyphenol-stabilized CeO_2 nanoparticles using *Camellia sinens* leaves xtract and evaluated the death rate, respiratory rate, blood pressure, and body temperature in a lipopolysaccharide (LPS)-induced sepsis model. The results demonstrated that the CeO_2 treatment significantly decreased the level of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and high-mobility group protein 1 (HMGB1), as well as the orientation of inducible nitric oxide synthase (iNOS), an NF-kB transcriptional bustle. All these changes resulted in reduced hepatic damage and weakened systemic swelling. However, ordinary CeO_2 nanoparticles can not selectively target the mitochondria, a key ROS production site in cells. Thus, it may not directly and efficiently remove excessive ROS, requiring improvement. Yu et al[41] first synthesized triphenylphosphine-modified CeO_2 nanoparticles (TCeria) to target the mitochondria, followed by the synthesis of ROS-responsive grafts.Then, atorvastatin and TCeria were co-loaded into the core of ROS-responsive grafts to construct the drug delivery nanosystems (Atv/PTP-TCeria). Results showed that the prepared drug delivery nanosystems could be effectively distributed to the mice's kidneys with a sepsis-induced acute injury. Additionally, the retention time was prolonged. At 24 and 48 h after administration, TNF-α levels in renal tissue of Atv/PTP-TCeria treated mice were significantly lower, compared with the PBS group. At the same time, Atv/PTP-TCeria treatment can effectively improve renal function, alleviate renal tubular injury, and reduce renal tissue apoptosis and necrosis. Since LPS can cause liver injury in mice, the levels of serum aspartate aminotransferase and alanine aminotransferase were evaluated to confirm the compatibility. There was no significant difference between the control group and Atv/PTP-TCeria group, suggesting that no serious adverse effect occured in the mouse liver during the treatment. This strategy provided a new idea for precisely scavenging ROS in the mitochondria of inflammatory cells.

Anti-Inflammatory Drug Delivery Nanosystems

When the human body is invaded by exogenous pathogens, lesions (tumors), or trauma, neutrophils are activated. Through self-deformation through the vascular barrier, neutrophils are enriched in the lesion.However, their survival time is short. After death, they release a large number of inflammatory factors and cause an excessive immune response. Additionally, during the human immune response, neutrophils can not distinguish between threats and non-threats. While releasing different toxic proteins to attack bacteria and other invasive pathogens, neutrophils can also kill healthy human cells, tissues, and organs, leading to various inflammatory diseases. Based on overexpressed FC-γ on the surface of activated neutrophils, Zhang et al[42] linked doxorubicin to bovine serum albumin (BSA) via pH-sensitive bonds to prepare nanoparticles (doxorubicin-hydrazone-bovine serum albumin, DOX-hyd-BSA), which can induce apoptosis.[43] The obtained nanoparticles could target and recognize activated neutrophils. When they reach the activated neutrophils, they are stimulated by low pH, releasing anti-cancer drugs, promoting apoptosis, avoiding neutrophils' accumulation in tissues, and improving the occurrence of many inflammatory diseases, such as sepsis. Additionally, they found that mice treated with the prepared nanoparticles resumed levels of neutrophils and cytokine contents at 72 h comparable to the healthy mice. This indicated that DOX-hyd-BSA nanoparticles do not inhibit neutrophil production and function in bone marrow.

Lipopolysaccharide (LPS), the main structural component of the Gram-negative bacteria outer membrane, can bind to Toll-like receptor 4, triggering transcription factors (such as nuclear factor kappa beta (NF-κB) family) signals to produce inflammatory responses, the main sepsis characteristic. Curcumin (*Curcuma longa*) is a natural

bisphenol compound extracted from the *Curcuma longa* rhizome. It has many biological and pharmacological properties such as anti-cancer and anti-inflammation. However, because of its poor water solubility, fast degradation, and low bioavailability, curcumin has a limited therapeutic effect. Therefore, Wang et al[44] prepared curcumin-loaded solid lipid nanoparticles and evaluated their therapeutic potential for sepsis. The in vivo imaging results showed that in transgenic mice with LPS (3 mg/kg) intraperitoneal injection causing a corresponding inflammatory response, a maximum fluorescence intensity after 3 hours trend was detected, then gradually weakened. Intraperitoneal injection of curcumin-loaded solid lipid nanoparticles (30 mg/kg) could significantly inhibit the fluorescence expression intensity for 3 h and was equivalent to dexamethasone. The results of an enzyme linked immunosorbent assay showed that the curcumin-loaded solid lipid nanoparticles could significantly reduce IL-6 and TNF-α inflammatory factors in the serum of mice and IL-1 β. Additionally, IL-10 expression was significantly increased. The hematoxylin-eosin staining results showed that this nanosystem could effectively attenuate glomerular and tubular injury and reduce hepatic necrosis compared with the free curcumin group. Finally, Western blot results showed that it could significantly inhibit the Toll-like receptor-4 (TLR-4), TLR-2, NF-κB) in lymph nodes and TNF-α protein expressions. These results provided new insights for sepsis treatments.

Other Drug Delivery Nanosystems

Recent studies have shown that the cell free DNA (cfDNA) content increaseds in sepsis patients' blood and can be recognized by the TLR-9 receptor of immune cells, resulting in an abnormal immune response. The TLR-9 knockout sepsis mice mortality is reduced, as the inflammation in vivo. Therefore, cfDNA neutralization or elimination may reduce sepsis organ damage by immune response regulation, inhibiting the pro-inflammatory cascade and cytokine storm. Based on this, Dawulieti et al[45] synthesized three polyethyleneimine (PEI) functionalized and biodegradable mesoporous silica nanoparticles (MSN-PEI 25K, MSN-PEI 800, and MSN-NH_2) with different charge densities using PEI, and investigated their ability to scavenge cfDNA. The results showed that MSN-PEI had better therapeutic and protective effects than PEI. The therapeutic effect of MSN-PEI 25K with a high charge density on sepsis mice was better than MSN-PEI 800 with a low charge density. MSN-PEI 25K with a high charge density had a stronger nucleic acid binding ability, stronger inhibitory effect on the cfDNA induced inflammatory response, higher targeting, better retention of inflammatory sites in septic mice, and improved anti-inflammatory effects. Moreover, they found that MSN-PEI 25K exhibited an increased macrophages inhibitory concentration of 61.45 μg/mL compared with soluble PEI 25K (22.98 μg/mL). Additionally, MSN-PEI 25K could significantly reverse the elevated serum alanine aminotransferase, aspartate aminotransferase, bilirubin, blood urea nitrogen, creatinine and creatine kinase, indicating reduced toxicity to macrophages and major organs. Therefore, it represents a more efficient and safer cfDNA scavenger.

MicroRNAs (miRNAs) are non-encoding RNAs with 21–25 nucleotides, which affect gene posttranscriptional regulation by causing gene instability and preventing mRNA translation.[46–48] MiR-126 is the most abundant miRNA in endothelial cells. Studies have shown that high expression of microRNA-126 (miR-126) treatment of endothelial progenitor cells can improve the survival rate of septic mice with cecal ligation and perforation. However, due to the ubiquitous rapid degradation of ribonuclease, it is challenging to transfer miRNAs to cells in vitro and in vivo. Jones Buie et al[49] prepared a drug delivery system composed of deacetylated poly-N-acetyl glucosamine nanoparticles loaded with miRNA-126-3p or miRNA-126-5p. The constructed nanoparticles effectively encapsulated miRNAs and prevented their migration in agarose gel, thereby protecting miRNA from Ribonuclease A (RNase A) degradation. Nearly 67% of the sepsis mice treated with the complex survived at day 7, while only 25% of the untreated mice survived. Therefore, this drug delivery nanosystem significantly improved the survival rate and reduced inflammatory cytokines response. In addition, they also determined the impact of deacetylated poly-N-acetyl glucosamine nanoparticles loaded with miRNA-126 (DEAC-pGlcNAc:miR-126) on cellular metabolic activity. No significant differences could be observed between the untreated group and the DEAC-pGlcNAc:miR-126-treated group.

All the drug delivery nanosystems developed for sepsis treatment are listed in Table 1.

Conclusions

Sepsis is a systemic inflammatory response syndrome caused by infection, with a high incidence. It has become the main cause of death for intensive care unit (ICU) patients in China and seriously threatens human health. Although the underlying sepsis pathogenesis is unclear, it is mainly related to the host's aggressive immune

Table 1 The Drug Delivery Nanosystems Developed for Sepsis Therapy

Mechanism	Drug Delivery Nanosystems	Active Compounds	Results	References
Antibacterial	Polycaprolactone nanoparticles	Moxifloxacin and rutin	Demonstrated a good antimicrobial activity against *E. coli*	[50]
	S-thanatin functionalized liposomes	Levofloxacin	Significantly enhanced the bacterial internalization, resulting in the synergistic effect of antibiotic and anti-bacterial peptide	[25]
	Chitosan-mastoparan nanoconstruct	Mastoparan	Exerted lower MIC90 (4 μg/mL), reduced bacterial colony count, and had a synergistic bactericidal effect against MDR clinical *A. baumannii* isolates.	[51]
	Anti-mouse ICAM-1 antibody modified pH/enzyme-sensitive nanoparticles	Ciprofloxacin and an (2-[(aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide	Effectively eliminated the invasive bacteria and alleviated the inflammatory reaction, thus improving the survival rate.	[31]
	Vitamin lipid nanoparticles	Antimicrobial peptide and cathepsin B mRNA	Effectively reduced the number of drug-resistant bacteria in the body, and improved the host's body function.	[32]
	Spherical, prolate ellipsoidal and oblate PLGA nanoparticles coated with red blood cell membrane	_	Had a lower systemic elimination rate, longer half-life, and stronger bacterial toxins detoxification ability.	[33]
	Graphene-oxides-based drug delivery nanosystems	_	Exerted strong bacterial killing ability	[34]
	Two-color gold and multilayer magnetic nanoparticles with giant amplifications of PA and PT contrasts were functionalized with an antibody cocktail for molecular targeting	_	Integrated in vivo multiplex targeting, magnetic enrichment, signal amplification, multicolor recognition, and feedback control	[52,53]
Anti-oxidative	WS2, MoSe2, and WSe2 nanosheets	_	Effectively removed ROS and RNS, improved severe sepsis mice survival rate.	[35]
	Ceria nanoparticles	Atorvastatin	Reduced hepatic damage and systemic swelling.	[40,41]
Anti-inflammatory	Doxorubicin linked to BSA via pH-sensitive bonds	Doxorubicin	Targeted the activated neutrophils and showed responsive release behavior of doxorubicin to promote apoptosis of neutrophils.	[43]
	Solid lipid nanoparticles	Curcumin	Significantly reduced the inflammatory cytokines, reduced organ damage, inhibited the TLR-4, TLR-2, NF-κB in lymph nodes.	[44]
	Silicium dioxide	Antibiotic	Considerably increased animals` survival rate and intensity of inflammatory system reaction.	[54]
	Chitosan-coated curcumin nanocrystals	Curcumin	Up-regulated levels of Nrf2, SOD and GST, down-regulated NF-κB, leading to reduced cytokine secretion.	[55]

(*Continued*)

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Table 1 (Continued).

Mechanism	Drug Delivery Nanosystems	Active Compounds	Results	References
Others	MSN-PEI 25K, MSN-PEI 800, and MSN-NH_2	–	MSN-PEI 25K with high charge density had a stronger nucleic acid binding ability, stronger inhibitory effect on cfDNA-induced inflammatory response.	[45]
	Deacetylated poly-N-Acetyl Glucosamine Nanoparticles	miR-126	Nearly 67% of the sepsis mice survived at day 7	[49]
	Amorphous aluminum hydroxyphosphate nanoparticles	–	Elicited long-lasting and enhanced humoral immunity, and provided protection in *S. aureus* sepsis mice models.	[56]

Abbreviations: MIC90, minimal inhibitory concentration; MDR, multidrug-resistant; ICAM-1, intercellular adhesion molecule; PLGA, poly lactic-co-glycolic acid; PA, pulmonary atresia; PT, prothrombin time; WS2, tungsten disulfide; MoSe2, molybdenum selenide; WSe2, tungsten diselenide; ROS, reactive oxygen species; RNS, reactive nitrogen species; BSA, bovine serum albumin; TLR-2, toll-like receptor-2; TLR-4, toll-like receptor-4; TLR-9, toll-like receptor-9; NF kappa B, nuclear factor kappa beta; Nrf2, nuclear factor erythroid-2-related factor 2; SOD, superoxide dismutase; cfDNA, circulating free DNA; MSN, mesoporous silica nanoparticles; PEI, polyethyleneimine.

response. Therefore, sepsis and its complications are mainly controlled and treated using antibacterial, anti-inflammatory, and antioxidant drugs. However, in the organism, small-molecule drugs have disadvantages, such as a too-fast clearance rate, low utilization, high toxicity and side effects, which can lead to ineffective treatments. The great advancement in nanotechnology has brought a new technological revolution for small-molecule drugs delivery.[57–59] Based on action mechanisms, this paper reviewed the drug delivery nanosystems recently used for sepsis treatment. By directly targeting bacteria or inflammatory cells, these drug delivery nanosystems can significantly improve their antibacterial, anti-inflammatory, and antioxidant abilities, reducing the toxicity and side effects of long-term, high-dose administration.

There are some commercial nanoformulations for the treatment of infection, including liposomal amphotericin B (AmBisome®), amphotericin B lipid complex (Abelcet®), nanosilver et al. Amphotericin B with a broad antifungal spectrum, has strong antibacterial effect on *Candida, Aspergillus*, and fungus. Moreover, it was reported that it had almost no drug resistance in the past.[60] However, amphotericin B deoxycholate (AmB), the first formulation used in the clinic, has been associated with some drawbacks, including nephrotoxicity, low solubility, and low bioavailability (<0.9%).[61] In contrast, nanoformulations of amphotericin B, such as liposomal amphotericin B, tend to prolong the circulation time, resulting in distribution into many different organs (mainly in the spleen and liver) rather than a large accumulation in kidneys. In addition, liposomal amphotericin B significantly changed the pharmacokinetic parameters, as reflected by higher C_{max} and the area under the curve.[62] Compared with conventional deoxycholate amphotericin B, the tolerated doses of amphotericin B-based nanoformulations improved from 1.5 mg/kg of body weight/day to 15 mg/kg.[63] These improvements reduced the toxicity without decreasing the therapeutic effect of amphotericin B, promoting the progress of drug delivery nanosystems for sepsis treatment. Detailed information of commercial nanoformulations for sepsis treatment is listed in Table 2.

Limitations and Future Perspective

Above all, it is still difficult to translate these new findings into clinical practice. The reasons were listed as below.

First, before entering the target site, the drug delivery nanosystem needs to overcome many obstacles, such as avoiding the reticuloendothelial system phagocytosis,[86–88] and nanomaterial protein corona.[89,90]

Table 2 Commercial Nanoformulations for Sepsis Treatment

Name	Company	Nanocomposition	Application	Clinical Stage	Ref.
Abelcet	Enzon Pharmaceutical (Sigma-Tau Pharmaceuticals)	Liposomal amphotericin B	Fungal infection	Commercially available	[64]
AmBisome	Gilead Sciences	Liposomal amphotericin B	Fungal infection	Commercially available	[65,66]
Amphotec	Sequus Pharmaceuticals	Liposomal amphotericin B	Fungal infection	Commercially available	[64]
Fungisome	Lifecare Innovations	Liposomal amphotericin B	Fungal infection	Commercially available	[67
Neulasta	Amgen Inc.	Filgrastim-bound polymeric NPs	Fibrile neutropenia	Commercially available	[68,69]
LogiCath AgTive	Smiths Medical International	Nanosilver	Antimicrobial coating device	Commercially available	[70]
PerOssal	Aap Impantate	Calcium sulfate and nanoparticulate hydroxyapatite Composite	Antibiotic delivery	Commercially available	[71]
Spi-Argent	Spire Biomedical Corporation	Nanosilver	Antimicrobial coating device	Commercially available	[72–74]
TAK-242	Takeda Global Research & Development Center, Inc.	Resatorvid emulsion	Sepsis	Commercially available	[75–77]
PEV7	Pevion Biotech Ltd	r-SAP2 virosomal vaccine	Recurrent vulvovaginal candidiasis	Commercially available	[78,79]
Cytosorb	CytoSorbents Corporation	Polymeric nanobeads	Hemoadsorption device for septic shock	Commercially available	[80–84]
MAT2501	Matinas Biopharm	Amikacin-loaded lipid nanocrystals	Bacterial infection	Commercially available	[85]

Note: Adapted from Papafilippou L, Claxton A, Dark P, Kostarelos K, Hadjidemetriou M. Nanotools for sepsis diagnosis and treatment. *Adv Healthc Mater.* 2021; 10(1): e2001378. © 2020 The Authors. *Advanced Healthcare Materials* published by Wiley-VCH GmbH[57].

Second, overcoming bacterial resistance still complicate antibacterial drug delivery nanosystem preparation. For example, bacterial biofilm, a systematic bacterial growth organization, helps bacteria adapt to environmental pressure by adjusting their metabolism and developing strong drug resistance.[91,92] How to use bacterial biofilms to infect a microenvironment with high acidity, hypoxia, and ROS content in tissues, and how to design a drug delivery nanosystem with high efficiency to destroy the biofilm still present some challenges. Additionally, although most bacteria are recognized and killed by phagocytes, some can survive in phagocytes.[93] Therefore, how to construct phagocytes that can actively target the infected ones and realize antibiotics intracellular delivery should also be the focus of antibacterial drug delivery nanosystem development.

Third, the existing drug delivery nanosystem treatment modes are too unique. Sepsis is fierce, often starting from multiple pathways, destroying the body's function.[94,95] Therefore, it is necessary to develop drug delivery nanosystems with more functions to kill bacteria, inhibit inflammatory cascades and monitor curative effects.

Overall, through continuous optimization, drug delivery nanosystems still present great potential for precise sepsis treatment.

Abbreviations

ICAM-1, Intercellular adhesion molecule 1; GO, Graphene oxide; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; TMD, Transition Metal Dichalcogenide; CAT, Catalase; LPS, Lipopolysaccharide; TNF-α, Tumor necrosis factor-α; IL-1β, IL-6, IL-10, Interleukin-1, interleukin-6, interleukin-10; HMGB1, High mobility group protein 1; iNOS, Inducible nitric oxide synthase; TCeria, Triphenylphosphine modified Cerium oxide nanoparticles; Atv/PTP-TCeria, Atorvastatin and TCeria were co-loaded into the core of ROS responsive grafts to construct the drug delivery nanosystems; miRNAs, Micro RNAs; PEI, Polyethylenimine; RNase A, Ribonuclease A; MIC, Minimal inhibit concentration; MDR, Multidrug resistant;

PLGA, Poly lactic-co-glycolic acid; PA, Pulmonary ATRESIA; PT, Prothrombin time; WS2, Tungsten disulfide; MoSe2, Molybdenum Selenide; WSe2, Tungsten diselenide; BSA, bovine serum albumin; TLR-2, TLR-4, TLR-9, Toll-like receptor-2, Toll-like receptor-4, Toll-like receptor-9; NF kappa B, Nuclear factor kappa beta; Nrf2, Nuclear factor erythroid-2-related factor 2; SOD, Superoxide dismutase; cfDNA, Circulating free DNA; ICU, Intensive care unit; AmB, Amphotericin B deoxycholate; AmBisome, Amphotericin B; r-SAP2, Candida Albicans; Abelcet, Amphotericin B lipid comlex.

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Disclosure

The authors report no conflicts of interest in this work.

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