



## Recent advances in nanomedicine therapy for bacterial pneumonia

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### ABSTRACT

Bacterial pneumonia is one of the most common infectious diseases, a great threat to the health of children and the elderly. In the clinic, due to the extensive use of antibiotics, multi-drug-resistant bacteria have increased in large numbers, seriously affects the treatment of patients with bacterial pneumonia. With the development of nanomedicine, it shows great potential in the treatment of bacterial pneumonia. In this review, it initially comprehensively describes the pathological process of bacterial pneumonia and the current status of its clinical treatment. Then it summarizes the strategies of nanomedicine for the treatment of bacterial pneumonia, including inorganic nanomaterials, polymer nanoparticles, natural source nanomaterials and artificial antimicrobial peptides, with a focus on novel nanomaterials for the treatment of bacterial pneumonia (biomimetic nanomaterials, nanovaccines and genetically engineered nanomaterials). Finally, the prospect of nanomedicine for bacterial pneumonia therapy is discussed in the hope of providing new ideas for the clinical treatment of bacterial pneumonia.

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### 1. Introduction

Pneumonia is an infection of the lungs caused by bacteria, viruses or other microorganisms, with bacterial infection being the most common [1,2]. Common symptoms of bacterial pneumonia include coughing, coughing up sputum, and in severe cases, shortness of breath and dyspnea. It has a high mortality rate in children and the elderly, also people who are immunocompromised (autoimmune diseases, immunosuppressive drugs), and people with chronic respiratory diseases [3].

Currently, antibiotics are still the first-line drugs for the clinical treatment of bacterial pneumonia. Traditional antibiotics can effectively inhibit most bacteria, thus alleviating the clinical symptoms of bacterial pneumonia. However, due to the misuse of antibiotics, traditional antibiotics are ineffective in the treatment of multi-drug resistant bacteria. Thus, antibiotic resistance has become a hot issue for researchers around the world [4–6]. In addition to this, the poor targeting of antibiotics enhances the systemic toxic effects and the bioavailability of traditional antibiotics is low due to the

anatomical structure of the lungs [7]. All of these contribute to the poor prognosis of bacterial pneumonia. Consistent with antibiotic therapy, supportive therapy [8], and Chinese medicine therapy [9] also have many limitations.

In order to solve the above problems for bacterial pneumonia, there is an urgent need to develop new therapeutic methods. With the development of nanotechnology, nanomaterials have excellent antimicrobial effects [10] and are precisely targeted to the lungs [11]. Specifically, for some nanomaterials, it is possible to enhance the bactericidal effect by enhancing the body's immune response at the same time as the bactericidal effect, and this approach provides a new direction for the treatment and prognosis of bacterial pneumonia [12]. In the future, nanomedicines hold the promise of becoming an important tool in the treatment of bacterial pneumonia. In this review, we review the main pathological mechanisms of bacterial pneumonia, the current status of clinical treatment of bacterial pneumonia, and the treatment of bacterial pneumonia based on nanomedicines, hoping to provide new ideas for the clinical development of bacterial pneumonia.

### 2. Pathological process of bacterial pneumonia

Bacterial pneumonia is the most common type of pneumonia, which mainly includes *Streptococcus pneumoniae*, *Staphylococcus*

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*aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and other pneumonias, and poses a great threat to the health of children and the elderly [13]. The pathological process of bacterial pneumonia is divided into three phases: the congestive phase is the first phase of the pathological process of bacterial pneumonia, with capillary congestion and dilatation, and plasma exudate in the alveolar cavity. The second phase is the solid phase, with the further development of inflammation, and a large amount of fibrous exudate and erythrocytes ooze out. And then the exudate is dominated by neutrophils and monocytes, a large number of bacteria are phagocytosed, and a large number of erythrocytes are disintegrated, which finally results in the occurrence of lung tissue solid changes. The dissipation phase is the last phase, the leukocytes and bacteria die, and are discharged with sputum, and the lung tissue returns to normal state [14–17]. Most of the pathological processes of bacterial pneumonia are accompanied by various degrees of destruction of the alveolar walls, as well as necrosis of lung tissue and the formation of lung abscesses. The pathogenesis involves a variety of complex physiologic processes, and this part will detailed introduce the processes of infection, inflammation, and immune response.

### 2.1. Infection

Bacteria usually enter the lungs through inhalation of droplets from an infected person, contact with contaminated objects, or self-infection. When bacteria enter the lungs, they attach to the bronchial and alveolar epithelial cells, utilize their surface structures (e.g., cilia and adhesins) to begin colonizing the lungs [18].

### 2.2. Inflammation

Inflammation is a defense response by the body to clear pathogens and promote tissue repair following injury [19–23]. When bacteria enter the lungs through the respiratory tract, the host's immune system recognizes bacterial-specific pathogen-associated molecular patterns (PAMPs) (e.g., bacterial cell wall components, exotoxins, peptidoglycans, and lipopolysaccharides) via pattern recognition receptors (PRRs). When PRRs recognize bacterial components, they activate downstream signaling pathways (e.g., nuclear factor kappa-B (NF- $\kappa$ B) pathway), leading to intracellular signaling. These signals prompt the cell to produce and release inflammatory mediators (e.g., cytokines and chemokines). For activated immune cells (e.g., macrophages and dendritic cells (DCs)), they release a variety of inflammatory mediators including cytokines: tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), etc., which promote inflammatory responses, recruit other immune cells, and modulate immune responses, and chemokines: monocyte chemoattractant protein-1 (MCP-1), which attracts other immune cells (e.g., neutrophils, monocytes) to the site of infection. Although the inflammatory response is designed to clear the infection, an excessive inflammatory response may result in damage to host tissues. Excessive release of inflammatory mediators and activation of immune cells may lead to cell death and necrosis of lung tissue, resulting in the formation of exudate and purulent secretions in the alveoli [24].

### 2.3. Immunization

The mechanism between bacterial pneumonia and immune response is a complex interactive process involving the response and regulation of host immune system to bacterial infection. Neutrophils are the first immune cells to reach the site of infection after activation of inflammatory response and clear the infection by phagocytosis of bacteria and release of antimicrobial substances

such as lysozyme and reactive oxygen species (ROS). After phagocytosis of bacteria, macrophages can activate an adaptive immune response through antigen presentation, and DCs migrate to lymph nodes and activate specific T cells (e.g., CD4<sup>+</sup> T and CD8<sup>+</sup> T cells) after capturing and processing bacterial antigens. After clearing the bacteria, some of the T and B cells are converted into memory cells that can rapidly generate an immune response when the same infection occurs again [25–28].

According to the above, the pathologic process of bacterial pneumonia involves multiple cellular and molecular mechanisms, and these processes contribute to a better search for potential therapeutic targets.

## 3. Current clinical therapy of bacterial pneumonia

According to World Health Organization (WHO), pneumonia is one of the leading causes of death worldwide, especially among children and the elderly. There are approximately millions of pneumonia cases each year, of which bacterial pneumonia accounts for a significant proportion. The incidence of bacterial pneumonia increases significantly in children and the elderly due to decreased immune function. The current state of clinical treatment of bacterial pneumonia mainly includes antibiotic treatment, supportive therapy, and immunotherapy.

### 3.1. Antibiotic treatment

For community-acquired pneumonia (CAP), empiric antibiotics are usually selected based on the patient's age, comorbidities, and severity. Commonly used antibiotics include macrolides (e.g., azithromycin), penicillins (e.g., amoxicillin), and respiratory fluoroquinolones (e.g., levofloxacin). For hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), these types of pneumonia are usually caused by drug-resistant bacteria, making the treatment options more complex. Commonly used antibiotics include cephalosporins, carbapenems, fluoroquinolones, and polymyxins, which usually need to be adjusted based on the results of bacterial susceptibility testing. Particularly, specific antibiotics (e.g., vancomycin or rifampin) may be required for drug-resistant bacterial infections including methicillin-resistant *Staphylococcus aureus* (MRSA) and drug-resistant *Streptococcus pneumoniae* [29–32].

### 3.2. Supportive therapy

Supportive therapy for bacterial pneumonia aims to relieve symptoms, improve the overall status of patients, and promote recovery. For patients with hypoxemia, oxygen is provided using nasal cannulae and face masks, thereby improving the patient's oxygenation status and reducing respiratory distress. For critically ill patients, mechanical ventilation support may be required, especially for acute respiratory distress syndrome (ARDS). Replenish fluids by intravenous infusion are needed by the patient, especially in cases of fever, sweating, or loss of appetite, thereby maintaining proper water balance, and preventing dehydration and electrolyte disturbances. On the other hand, it is possible to use nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or acetaminophen to control pain and lower body temperature, which can also relieve chest pain and fever due to pneumonia. Similarly, inhaling saline or bronchodilators using a nebulizer also helps to relax the airways and dilute sputum to clear airway secretions, and improve ventilation. And implementation of respiratory therapy and physical rehabilitation can help the patient gradually regain strength and be able to improve lung function and exercise capacity [33–35].

### 3.3. Immunotherapy

Immunotherapy for bacterial pneumonia mainly focuses on helping to fight the infection by boosting the host's immune response. Vaccination against specific bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) can prevent the development of bacterial pneumonia. They provide protection by stimulating the body to produce a specific immune response [36]. In addition to this, cellular therapies can also offer some extra advantages. In some cases, immune cells (e.g., T cells or natural killer (NK) cells) can be extracted from the patient's body, expanded *in vitro*, and then infused back into the patient's body to enhance his or her ability to fight infection [37]. However, immunotherapy in the treatment of bacterial pneumonia is still in the research and development stage, and the precise application and effectiveness may vary according to individual differences.

In clinical practice, a combination of antibiotic therapy, supportive therapy and immunotherapy is usually required to achieve the best therapeutic effect.

## 4. Nanomedicine based therapeutic strategies

Bacterial pneumonia is an inflammation of the lungs caused by bacterial infection, and common causative organisms include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Legionella pneumophila*, and *Escherichia coli*. In recent years, the problem of drug resistance in bacterial pneumonia has become increasingly serious due to the misuse of antibiotics. And bacteria acquire resistance to antibiotics through genetic mutation, and also can acquire drug-resistant genes from other bacteria through splicing, transduction or transformation. Some bacteria are able to form biofilms in the body to increase their resistance to antibiotics. The emergence of drug-resistant bacteria makes conventional antibiotic treatment less effective, leading to treatment failure, prolonged illness and even increased mortality. Therefore, there is an urgent need to develop new drugs to treat bacterial pneumonia [38]. Nanotechnology based therapeutic strategies are a promising area that can improve existing approaches [39,40]. Therefore, an increasing number of nanomedicines are currently under development, which demonstrates the potential for the treatment of bacterial pneumonia. Herein, we will discuss nanomedicines that have recently been used, and those that hold promise for future use in the treatment of bacterial pneumonia. All nanomedicines we summarized are shown in Table S1 (Supporting information).

### 4.1. Inorganic nanomaterials

As we all know, inorganic metallic materials are composed of metals and their compounds with excellent mechanical properties, good corrosion resistance, stability and biocompatibility [41,42]. Nowadays, more and more inorganic metallic materials are applied in clinic. For example, they can be used as bioactive glass to promote bone regeneration in bone defect repair and bone grafting surgery [43]. And silver amalgam can be used as dental filling material due to its good wear resistance and corrosion resistance. Meanwhile, silver and copper nanoparticles (NPs) are commonly used in wound dressings and antimicrobial coatings due to their excellent antimicrobial properties [44–47].

#### 4.1.1. Single inorganic nanomaterials

Recently, researchers have discovered a composite nanomaterial composed of copper and manganese (Fig. 1) [48]. The material is sensitive to aerobic bacteria and can effectively induce the death of pulmonary aerobic bacteria by enhancing bacterial copper toxicity-like death. In *in vivo* experiments, the drug can effectively penetrate the lung mucus layer to reach the lungs di-

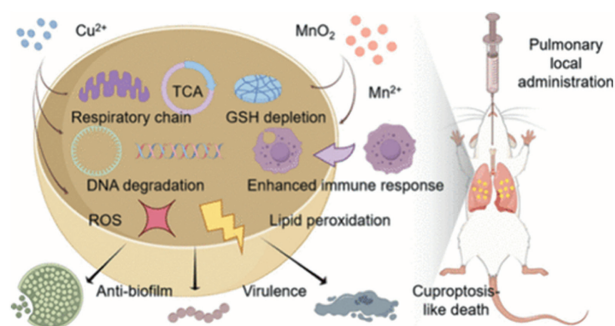


Fig. 1. The scheme of the stepwise construction of Cu-Mn NPs and a mucous permeable local delivery strategy. Copied with permission [48]. Copyright 2024, American Chemical Society.

rectly by localized drug delivery. Due to the acidic environment of the lungs, the copper ions are rapidly released, and further destroy the bacterial biofilm in synergy with manganese. This localized drug delivery system effectively avoids the generation of systemic toxicity. It can replace traditional antibiotics and achieve good therapeutic effects on aerobic bacterial infections. Besides, it has been demonstrated that bacterial pneumonia leads to inflammatory factor storm and severe lung injury. Therefore, scavenging pathogens, alleviating oxidative stress as well as anti-inflammation can be effective in the treatment of bacterial pneumonia. Liu *et al.* designed zinc hexacyanoferrate nanocatalysts (ZnPBA NCs) through zinc doped Prussian blue analogs [49], which were demonstrated to have broad-spectrum antimicrobial activity and good antioxidant properties *in vitro* experiments, and can largely reduce the inflammatory response while eliminating bacteria *in vivo* in a murine bacterial pneumonia model. In addition, Wu *et al.* designed a metal organic framework (MOF), which could consume  $H_2O_2$  secreted by bacterial infected lungs, thus reducing lung injury and preventing systemic bacteremia or sepsis [50].

#### 4.1.2. Inorganic nanosized drug delivery systems (DDSs)

In addition to the therapeutic means of replacing antibiotics with inorganic metallic materials, the therapeutic means of combining inorganic metallic materials and traditional antibiotics not only improves the problem of traditional antibiotic resistance, but also improves the targeting of traditional antibiotics, delivers the drugs accurately to the lungs, and mitigates systemic toxicity produced by the drugs [51]. Cheng *et al.* designed a drug delivery system for the treatment of polymyxins (CST)-resistant bacteria by modifying the combination of CST and nano-silver (Ag), a drug delivery system targeting the lungs, which showed good antibacterial effects, greatly reduced the inflammatory response, and demonstrated good biosafety and degradability, which provided a therapeutic direction for the treatment of pneumonia caused by CST-resistant bacteria [52]. In bacterial pneumonia therapy, the problems of multidrug-resistant bacteria and immune escape have been the focus of discussion among researchers. Xiu *et al.* designed a  $Fe_3O_4$  drug-carrying system. Along with sterilization,  $Fe_3O_4$  could induce macrophages into pro-inflammatory M1-type macrophages, thus activating the immune response and providing a novel means of nanomedicine in the process of synergistic biofilm elimination and immune activation therapy [53].

#### 4.1.3. Compositated nanomaterials

Some inorganic metal materials have good photodynamic or photothermal properties. The combination of photodynamic therapy/photothermal therapy (PDT/PTT) and inorganic metal materials plays a synergistic enhanced therapeutic effect, providing a new direction to replace traditional antibiotics [54,55]. In view of

the above, Duan *et al.* synthesized a multiple reusable and near-infrared (NIR) responsive zinc metalloporphyrin (DEP-BH@TSLs), which had good photothermal stability and could be repeated twice for NIR PTT [56]. Guo *et al.* synthesized a novel nanoscale antimicrobial composite (AuNRs@PBArPEGMA), which could alleviate the inflammatory response of macrophages induced by multi-resistant *Pseudomonas aeruginosa* (MRPA) infection by down-regulating mitogen-activated protein kinase (MAPK) and NF- $\kappa$ B signaling pathways. Meanwhile, the material had a good photothermal conversion ability, with the temperature increasing from 20 °C to 80 °C after about 5 min of NIR irradiation. This study provided a non-antibiotic therapeutic strategy for clinical use [57]. For deep tissue diseases such as bacterial pneumonia, ultrasound (US) induced sonodynamic therapy (SDT) has strong tissue penetration and is a promising therapeutic tool. Pan *et al.* designed an inhalable photosensitizing agents (ZTNs), which could be delivered precisely to the site of lung infection using intratracheal nebulized inoculation. *In vivo* experiments for immunodeficient mice with lung infection, it had confirmed that ZTNs treatment was able to prolong the survival rate more excellently, which could expand the application of inorganic acoustic sensitizers in nanomedicine [58]. In addition, it also expects that nanomaterials have good biocompatibility and less cytotoxicity along with good antimicrobial properties. Some researchers have proposed a therapeutic antimicrobial strategy for decocting nanomaterials. Aqueous formulations containing ferrous and polysulfide (Fe(II)S<sub>naq</sub>) were prepared by a decoction procedure using iron sulfide NPs (nFeS) as raw materials. This method showed significant antimicrobial efficacy against staphylococcus aureus and had essentially the same therapeutic efficacy as vancomycin treatment in mice, dramatically prolonging the survival of septic mice [59].

From the above, inorganic nanomaterials have significant antibacterial effects and can kill bacteria rapidly by destroying the cell membrane wall structure of bacteria. Compared with traditional antibiotics, inorganic nanomaterials have a unique antimicrobial mechanism that does not easily lead to bacterial resistance. For example, acoustic kinetic therapy utilizes US waves to activate acoustic sensitizers to produce ROS to kill bacteria, a method that eliminates multidrug-resistant bacteria while making it less likely to generate new resistance. However, inorganic nanomaterials are produced using relatively complex technologies, leading to high cost. This may limit their widespread clinical application, and the stability of inorganic nanomaterials is also an issue that needs to be considered. In practical applications, the stability of nanomaterials needs to be ensured to avoid affecting the therapeutic effect or adverse reactions due to the deterioration of nanomaterials. Inorganic nanomaterials have significant advantages in the treatment of bacterial pneumonia. but at the same time, they also face some challenges and shortcomings. With the continuous progress of technology and in-depth research, it is believed that inorganic nanomaterials will show a broader application prospect in the field of antimicrobial therapy.

#### 4.2. Polymer NPs

Polymer NPs are nanosized particles made from polymer materials [60]. Due to many excellent properties [61], they have a wide range of applications in the field of medicine, and can be used as drug carriers to mitigate systemic toxic effects by targeting drug delivery and controlling drug release, thus improving drug utilization and reducing side effects. Common polymer NPs used as drug carriers mainly include liposomes, polylactic acid-polyglycolic acid (PLGA) microspheres. These nanomaterials have been used in a variety of diseases treatment like tumors, inflammation, infections, etc. [62,63].

##### 4.2.1. Single polymer NPs

Polymer NPs have also shown excellent performance in bacterial pneumonia due to their superior properties [64]. Recently, it had been shown that polycarbonate had excellent broad-spectrum antimicrobial ability and killed bacteria more effectively than clinically used antibiotics. And the good degradability of this material reduced *in vivo* toxicity and minimized organ damage [65–67]. In addition to the degradable polymer NPs, polymer microspheres with lung targeting properties had also received extensive attentions. Lin *et al.* developed a staphylococcal lysine microsphere that could be targeted to the lungs, with good bactericidal effects against MRSA, which markedly improved survival and reduced inflammatory damage [68]. Fu *et al.* modified chitosan (CS) and hyaluronic acid (HA) on the surface of live lactobacillus rhamnosus to prepare polymeric NPs capable of targeting and modulating the microbiota, which could interact with the CD44 binding site on the surface of macrophages to target inflammatory macrophages, and improve the phagocytosis of macrophages by modulating the immune response. By combining immune-activating and antimicrobial synergy, it provided a new strategy for the treatment of patients with abnormal immune function [69].

##### 4.2.2. Polymer nanosized DDSs

In order to improve the therapeutic efficacy of traditional antibiotics, researchers have found that the use of polymers as carriers for antibiotics could improve the therapeutic efficacy of traditional antibiotics. Lu *et al.* prepared nitric oxide (NO)-sensitive nanomicelles (HA-NO-LF) by encapsulating traditional antibiotic levofloxacin (LF) with oleamide modified HA. *In vivo* experiments confirmed that the therapeutic efficacy of HA-NO-LF was better than that of LF [70]. Su *et al.* prepared a polymer DDS that prolonged the concentration of ciprofloxacin in alveolar macrophages (AM), significantly increasing the intracellular dose of the drug [71]. In patients with severe bacterial pneumonia, the large amount of mucus in the respiratory tract impedes the effective utilization of antibiotics. Therefore, Ren *et al.* crosslinked tobramycin (TOB) with oxidized soluble starch (OSS), to decompose mucus and enhance penetration due to the incorporation of poly(ethylene glycol), thereby increasing drug delivery efficiency and improving the utilization efficiency of conventional antibiotics [72]. Hussain *et al.* prepared a vancomycin-loaded nanoparticle with the cyclic 9-amino-acid peptide CARGGLKSC (CARG) that could be specifically targeted to the site of infection, which selectively accumulated in the lungs and skin of mice infected with staphylococcus aureus, with good targeting properties to minimize side effects [73].

In the last decade, polymyxin B (PMB) has been considered as the last line of defense in the treatment of Gram-negative bacteria. However, the occurrence of severe infectious diseases has hindered its application. Recently, it has been found that the use of polymers as carriers can ameliorate the side effects of PMB without decreasing its antimicrobial activity. Wu *et al.* combined HA with PMB, which was able to penetrate the limitations of the mucus and improve the bioavailability of PMB compared to free PMB [74]. Chai *et al.* delivered PMB via a polymer and found that the complex was not significantly toxic to cells, while retained the bactericidal ability of PMB, showing significantly less nephrotoxic and neurotoxic [75]. Meanwhile, Fang *et al.* developed nanoformulations with mucosal adhesion property for pulmonary delivery of antibiotics [76]. Flash nanocomplexation technique was employed for the preparation of CS-encapsulated tannic acid (TA)/polyvinyl alcohol (PVA)/PMB NPs (TPBC NPs) by non-covalent interactions of the components. TPBC NPs were prepared by a simple and reproducible procedure, providing a new strategy for lung delivery of antibiotics for the treatment of infectious acute pneumonia. The above suggests that drug-loaded nanocomplexes offer a way to reduce antibiotics' side effects without compromising their own an-

timicrobial activity, which provides the critical support for realizing clinical applications.

#### 4.2.3. pH-responsive polymer NPs

Bacterial infections are often accompanied by unique microenvironments, such as abnormal pH levels. In response to this phenomenon, researchers had designed pH-responsive polymer NPs composed of the cationic polymer Hex-Cys-DET and streptomycin to kill multidrug-resistant bacteria [77]. Zhang *et al.* synthesized pH-sensitive complexes (CIP-NPs-anti-ICAM-1) by combining an anti-inflammatory agent ((2-[(aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide) and an antibiotic (ciprofloxacin) [78]. Chen *et al.* prepared a pH-sensitive cluster NPs (anti-CD54@Cur-DA NPs) with active targeting ability of lung tissue [79]. The infectious microenvironment (IME) is an acidic environment with low pH. Thus, pH-responsive NPs can target the IME, and the drugs are released slowly at the site of infection, which can improve the bioavailability of antibiotics and reduce inflammation *in vivo*, effectively improving therapeutic efficacy.

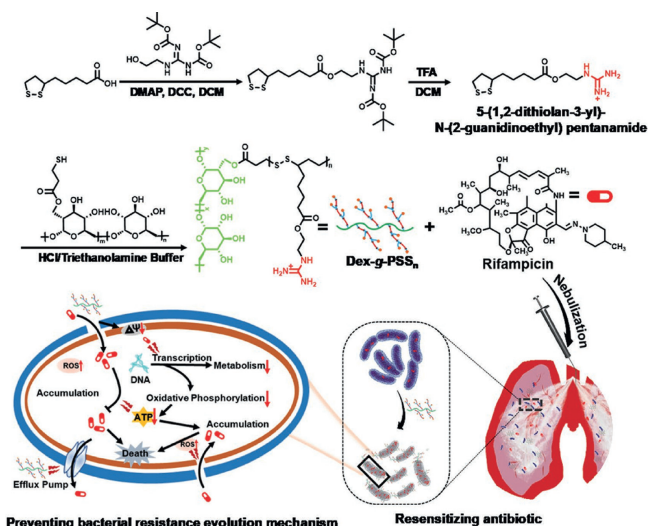
#### 4.2.4. Compositing polymer NPs

Polymers have excellent therapeutic effects as drug carriers and offer significant advantages in combination with other therapeutic methods. Polymers have a dual therapeutic effect when combined with inorganic metallic materials or other nanomaterials, and also with external stimuli like near infrared (NIR) irradiation, X-ray irradiation and US driven [80–82]. For example, Liu *et al.* developed a MOF (ZIF-8) containing vancomycin (Van) for lung targeting therapy, which could be easily recognized by CD44 due to the modification of HA, and thus be taken up by macrophages to efficiently clear MRSA [83]. Wang *et al.* synthesized a series of nanorods using calcium phosphate NPs and polymer particles for tigecycline delivery, which effectively reduced the resistance of *Klebsiella pneumoniae* to tigecycline [84]. Zhao *et al.* found that NIR irradiation effectively enhanced the antibacterial activity of the polymers, dispersing the biofilm by >80% [85]. Combined use of multiple therapeutic approaches has significant advantages. Zhu *et al.* encapsulated CS in ruthenium dioxide nanozymes, which enhanced the production of ROS under NIR irradiation, and the bactericidal effect was essentially the same as that of ciprofloxacin [86]. Significantly, to develop new antibiotics, some researchers have proposed a new strategy to sensitize multi-drug resistance (MDR) bacteria to existing antibiotics by synthesizing a novel cationic polysaccharide polymer that was able to increase intra-bacterial rifampicin (RIF) accumulation, and could prevent the bacteria from developing drug resistance. This study provided a new strategy to re-sensitize MDR to antibiotics (Fig. 2) [87].

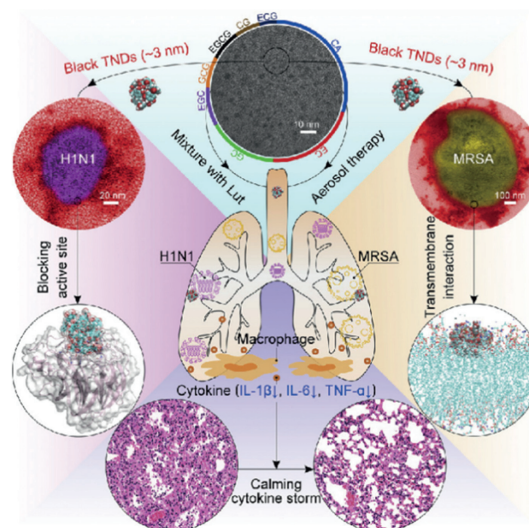
The advantages of polymer NPs for the treatment of bacterial pneumonia mainly include high stability, good controllability, excellent biocompatibility and targeted delivery. However, issues such as high technology cost need to be considered and addressed in practical applications to ensure that polymer NPs can be used safely and effectively for practical application.

#### 4.3. Natural source nanomaterials

Natural nanomaterials are nanoscale materials that are extracted or synthesized from nature. Because they are derived from natural substances, these materials are often considered to have a good safety profile [88]. Natural tea tree oil is an essential oil extracted from the leaves of tea tree. It has unique antibacterial and anti-inflammatory properties. Therefore, Zhang *et al.* prepared nanosized tea tree oil, which was delivered to the lungs by inhalation. It had demonstrated significant therapeutic effects against infectious pneumonia caused by drug-resistant *Acinetobacter baumannii* [89]. Currently, some researchers are focusing on



**Fig. 2.** Schematic illustration of cationic polysaccharide conjugates Dex-g-PSSn as antibiotic adjuvants in a multidrug resistance *Acinetobacter baumannii* (MDR-AB) pneumonia induced mouse model and associated preventative mechanisms toward bacterial resistance. Copied with permission [87]. Copyright 2022, Wiley-VCH.



**Fig. 3.** Schematic illustration of therapy for lethal H1N1-MRSA pneumonia through strategy of Chinese material-herbology black TNDs. Copied with permission [93]. Copyright 2021, Elsevier.

natural plant, which has good biocompatibility as well as anti-inflammatory and antioxidant properties due to the active components (e.g., polyphenols, flavonoids, amino acids) [90–92]. Li *et al.* extracted catechins from black tea to make natural nanodots with an average diameter of only 3 nm, which had good biosafety in piglets, and could be used in conjunction with lignans for rapid clearance of MRSA (Fig. 3) [93]. Zhou *et al.* utilized natural tea nanoclusters (TNCs) to inhibit  $\beta$ -lactamase and combined with amoxicillin sodium (Amo), showing significantly better therapeutic efficacy than monotherapy. It also confirmed that this therapeutic strategy had a good biosafety with no side effects in mice and piglets [94].

In addition, biomass derived carbon dots (CDs) have high fluorescence emission and good stability, which have a wide range of applications in the field of biomedical materials [95]. The extraction of biomass carbon source from nature has the advantages of being cheap and non-toxic. However, the selection of carbon source is an important aspect in the preparation of CDs. Researchers had

reported various biomass carbon sources. For example, Zhang *et al.* prepared guanidinium based carbon dots (G-CDs) from citric acid, dimethyldiallylammonium chloride, and polyhexamethyleneguanidine by melting strategy [96]. It was found that G-CD exhibited potent and long-term antibacterial activity as well as anti-biofilm activity with low potential to induce bacterial resistance. Zhao *et al.* synthesized quaternary ammonium carbon quantum dots (QCQDs) using a simple green "one-pot method". QCQDs were demonstrated to exhibit satisfactory antibacterial activity against gram-positive bacteria, including staphylococcus aureus, MRSA, staphylococcus epidermidis, listeria monocytogenes and enterococcus faecalis [97]. Poor management of bacterial pneumonia can cause acute lung injury (ALI) or the more serious form, ARDS. Researchers had also identified a number of anti-inflammatory compounds from herbs that might be beneficial in the treatment of ALI or ARDS. A biologically active and lung targeting lipid nanodrug, termed Ber-lipo, was developed by integrating bergamot peptide and dipalmitoyl phosphatidylcholine (DPPC) liposomes. For the first time, it was demonstrated that the new inhalable nanodrug (Ber-lipo) could target inflamed lungs and ameliorate ALI by reprogramming macrophage polarization to an anti-inflammatory state through inactivation of the Toll-like receptor 4 (TLR4)/myeloid differentiation primary response gene 88 (MyD88)/NF- $\kappa$ B pathway [98]. Sun *et al.* extracted the anti-inflammatory hydrophobic flavonol pachypodol (Pac) from Pogostemon cablin Benth, and embedded it in a liposome (Pac-lipo), which inhibited the TLR4-MyD88-NF- $\kappa$ B/MAPK pathway-mediated inflammation, and disrupted the lung barrier to improve ALI [99]. These findings may provide promising strategies for the treatment of ALI in the clinic.

Natural source nanomaterials are usually well biocompatible and can be better accepted by living organisms, reducing the occurrence of adverse reactions, and have also demonstrated significant antimicrobial effects, which can effectively reduce the bacterial loads and decrease the mortality of animals. However, there are some shortcomings of naturally sourced nanomaterials in the treatment of diseases, and the processing of natural products into nanomaterials requires complex techniques and processes, which may increase the production cost and time cost. Meanwhile, naturally sourced nanomaterials may be affected by environmental factors, such as temperature and humidity, further affecting their stability and therapeutic effects. In the future, with the continuous progress of technology and in-depth research, it is believed that naturally-derived nanomaterials will play a more important role in the treatment of bacterial pneumonia.

#### 4.4. Artificial antimicrobial peptides (AMPs)

AMP is an alkaline polypeptide substance induced from insects, which is characterized by strong alkalinity, heat stability and broad-spectrum antimicrobial activity [100]. Some studies have shown that AMPs have selective immune activation and regulation functions, and have good preventive and protective effects on sepsis [101–104]. AMPs include cationic peptides and neutral peptides, which are secreted by both Gram-positive and Gram-negative bacteria. It has been found that bacterial AMPs have good inhibitory effects on multi-drug resistant bacteria and no obvious toxic effects. Therefore, some researchers had linked AMPs with nanomaterials to prepare artificial AMPs and investigated the therapeutic efficacy of nanomedicine on bacterial pneumonia.

The lack of effective treatment for recurrent lung infections results in a large number of patients losing their lives each year [105]. Intravenous antibiotics are not effective in delivering antibiotics to the lungs and can have serious toxic effects. However, by inhalation administration, the drug's residence time can be prolonged in the lungs and the number of treatments can be reduced. A new nanosystem (M33-NS) obtained by capturing SET-

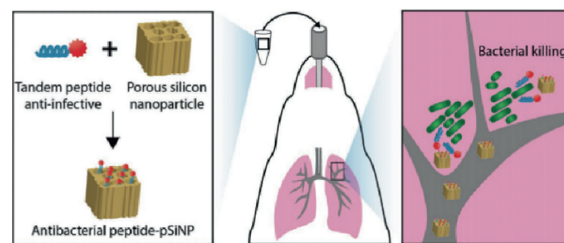


Fig. 4. Schematic illustration of designing materials composed of an anti-infective peptide cargo loaded in biodegradable porous silicon NPs for the treatment of lung infection models. Copied with permission [107]. Copyright 2017, Wiley-VCH.

M33 peptide on single-chain dextran NPs had shown good therapeutic effect on pneumonia caused by pseudomonas aeruginosa, and the tracheal nebulization delivery method allowed the drug to achieve a high dose and long lasting antimicrobial effect in the lungs [106]. Combination therapy with bacterial AMPs and polymer particles offers new directions for patients with pneumonia infected with pseudomonas aeruginosa. Porous silicon NPs (pSiNP) based nanosystem delivered the AMPs via the degradation of pSiNP, which improved biocompatibility while sterilizing the bacteria, and significantly increased survival rates (Fig. 4) [107]. Esculentin-1a (Esc peptide) extracted from frog skin, delivered by PLGA, showed good bactericidal effect against pseudomonas aeruginosa *in vitro* and *in vivo*, and also a long and stable bactericidal effect by tracheal administration [108]. To address the toxicity, short half-life, and poor therapeutic effect of AMPs against Gram-negative bacteria, researchers developed a novel AMP selected for the treatment of multidrug-resistant gram-negative bacteria with AMPs encapsulated in polymer NPs or lipid micelles, and found that both nanodrugs demonstrated good antimicrobial activity [109].

The advantages of artificial AMPs for the treatment of bacterial pneumonia mainly include broad-spectrum antimicrobial resistance, low drug resistance, and immunomodulatory effects. Nevertheless, there may also be limitations in the antimicrobial spectrum. Although artificial AMPs are generally considered safe, some of them may have adverse effects on humans, such as allergic reactions and toxicity, and thus require rigorous safety assessment and monitoring.

#### 4.5. Other novel nanomaterials

With the development of nanomedicine, some novel nanomaterials have also received extensive attention from researchers, such as biomimetic nanomaterials, nanovaccines and genetically engineered nanomaterials.

##### 4.5.1. Biomimetic nanomaterials

Biomimetic nanomaterials are cell membranes (erythrocyte, platelet, neutrophil, and macrophage membranes, *etc.*) wrapped around the surface of nanomaterials to form a core-shell structure [110,111]. This material not only retains the active substances on the surface of cell membrane, but also utilizes the good biocompatibility and permeability of cell membrane. In tumor therapy, biomimetic nanomaterials have shown great potentials [112]. It can significantly improve the biocompatibility and realize long-lasting circulation and targeted delivery [113].

As biomimetic nanomaterials continue to evolve in biomedical fields, some researchers have become interested in their effectiveness in the treatment of bacterial pneumonia. For example, Wang *et al.* extracted NK cell membranes, and wrapped them around the surface of an antibiotic to develop a biomimetic nano-antibiotic. The biomimetic antibiotic retained the TLR on the sur-

face of NK cell membrane, which enabled precise targeting of bacteria with excellent mucus penetration [114]. Zhang *et al.* encapsulated polymer NPs with neutrophil membrane, which acted synergistically with conventional antibiotics, and were able to rapidly and uniformly distribute them into the deep lung tissues, reducing the clearance of the nanomaterials by AM due to the encapsulation of neutrophil membrane [115]. It is well known that polydopamine (PDA) has excellent anti-inflammatory and antioxidant effects, and can consume excessive ROS [116,117]. Yin *et al.* wrapped macrophage cell membranes (CM) around the surface of oseltamivir phosphate (OP) loaded PDA, which could rapidly accumulate in a lung damage model of viral infection, and in an influenza A virus-infected mouse model. It finally confirmed that it could repair the lung damage, and improve pulmonary edema at the same time [118].

The biomimetic nanomaterial DDRs have demonstrated excellent performance for the treatment of bacterial pneumonia, and have a dual therapeutic effect on patients with bacterial pneumonia. Currently, some researchers have discussed the therapeutic efficacy of non-antibiotic treatments for bacterial pneumonia. Li *et al.* developed a bioresponsive silver peroxide ( $\text{Ag}_2\text{O}_2$ ) based nanovesicles, where  $\text{Ag}_2\text{O}_2$  NPs were firstly modified with bovine serum albumin and PDA, and then encapsulated with macrophage membranes (MM), which could be specifically targeted to the inflammatory tissues of lungs, with highly efficient antimicrobial and anti-inflammatory properties. This approach offered a promising therapeutic strategy for carbapenem resistant bacteria producing metallo- $\beta$ -lactamase (MBL) [119]. Hu *et al.* prepared antimicrobial particles (mFe-CA) with lung targeting properties by utilizing  $\text{Fe}_3\text{O}_4$ , which can be used as an iron inducing agent to induce iron death in MRSA, by wrapping a mixed cell membranes consisting of erythrocyte and platelet membranes around its surface, and by stimulating with US to achieve an effective controlled release effect. For *in vivo* experiments, there was no significant toxicity, and the survival rate of mice was improved [120]. The above study used a non-antibiotic approach to address the problem of antibiotic resistance and offered a promising future for lung-associated infections.

#### 4.5.2. Nanovaccines

Nanovaccines are novel vaccines that utilize NPs as carriers to enhance the body's immune response while exert antibacterial effects [121,122]. Recently, some researchers reported a nanovaccine encapsulated in bacterial outer membrane vesicles (OMVs) that enhanced immunotherapy for bacterial pneumonia. In *in vivo* experiment, the nanovaccine induced rapid activation of DCs in the lymph nodes of mice, which could stimulate the production of cytotoxic T cells to destroy bacteria in the body. It also activated the body to generate an immune response, which could prevent the risk of bacterial infection [123]. Currently, there are no effective clinical treatments for lethal bacterial lung infections such as pneumonic plague, and with the development of nanomedicine, new possibilities for this disease have been opened up. Ouyang *et al.* developed novel amino-modified mesoporous manganese silicate NPs (AMMSN) loaded with rF1-V10, which could be uptaken by DCs, and promote DC maturation by activating the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. This study provided a valuable strategy for patients with lethal bacterial pneumonia (Fig. 5) [124]. Du *et al.* also demonstrated similar effects by designing nanovaccines targeting multidrug-resistant (MDR) acinetobacter baumannii that efficiently killed bacteria in the lungs and bloodstream, and activated the immune response in mice [125].

Vaccination is now an increasingly attractive strategy to prevent antibiotic-resistant infections. Researchers had developed cellular nanodiscs made of bacterial outer membrane (OM-ND) as a

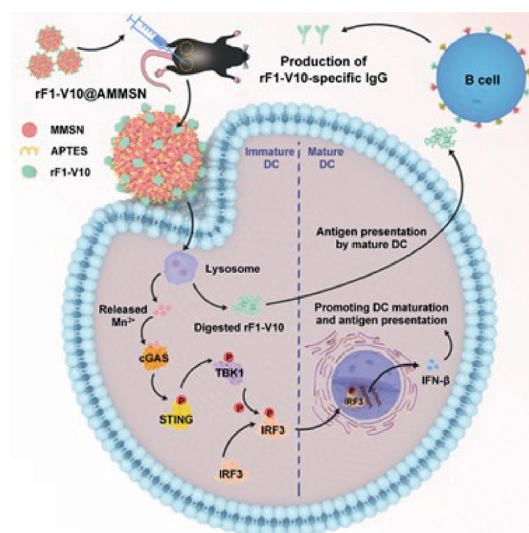


Fig. 5. Schematic illustration of the mechanism of rF1-V10@AMMSN-induced protection against *Y. pestis* infection. Copied with permission [124]. Copyright 2023, Wiley-VCH.

platform for antimicrobial vaccination. Using pseudomonas aeruginosa as a model pathogen, the resulting OM-ND effectively interacted with antigen presenting cells, exhibiting accelerated bacterial uptake and enhanced immunostimulatory capacities. Due to its small size, OM-ND could also be efficiently transported to lymph nodes after *in vivo* administration. As a result, the nanovaccine was effective in triggering efficient humoral and cellular immune responses against pseudomonas aeruginosa [126]. And Peng *et al.* reported a multi-antigen antimicrobial nanovaccine (AuNP@HMV@SPs) against *P. aeruginosa* infection. The vaccine induced robust humoral and cellular immune responses, leading to the destruction of bacteria. In a sepsis mouse model, it demonstrated that AuNP@HMV@SPs possessed excellent prophylactic efficacy, achieving 100% survival in sepsis [127]. With the continuous development of nanotechnology, nanovaccines show an increasingly important role in promoting personalized and precision medicine for bacterial pneumonia therapy [128,129].

#### 4.5.3. Genetically engineered nanomaterials

Genetically engineered NPs are nanoscale particles capable of delivering genes and genetic material to target cells with precision [130]. Tang *et al.* reported a macrophage targeted lipid NP (CRV/LNP-RNAs) co-loaded with MRSA-targeted chimeric antigen receptor (SasA-CAR) mRNA and CASP11 siRNAs, which were capable of precisely editing macrophages for the treatment of multi-drug-resistant bacteria caused by septicemia. The results demonstrated the potential of NPs to generate CAR-macrophages *in vivo* as a therapeutic platform for multi-drug resistant bacterial infections [131].

Since bacterial pneumonia is associated with increased localized inflammation, directing drugs to the site of inflammation may be a powerful therapeutic strategy. One of the common features of inflamed endothelial cells is the up-regulation of vascular cell adhesion molecule-1 (VCAM-1). Here, the specific affinity between very late antigen 4 (VLA-4) and VCAM-1 was exploited to produce biomimetic NP formulations capable of targeting inflammation. Genetically VLA-4 expressed cell membrane was coated on polymeric NP cores, and the resulting biomimetic NPs exhibited enhanced affinity for targeting cells overexpressing VCAM-1 *in vitro*. The anti-inflammatory drug dexamethasone was encapsulated in the nanoformulations and it was able to improve the delivery of payload to the inflamed lungs and exerted significant

therapeutic effects *in vivo*. Overall, this work took advantage of the unique benefits of biofilm coatings to engineer additional targeting specificity using naturally occurring target-ligand interactions. These engineered cell membranes allow the NPs to find the site of inflammation, and then release the drug inside the NP to treat the specific area of inflammation [132].

From the above, biomimetic nanomaterials can serve as a safe and efficient platform for targeted drug delivery. By homologous targeting cells that can escape capture by the immune system, therapeutic efficacy against bacterial pneumonia can be improved. Nanovaccines are often more highly targeted, and can precisely deliver antigens to the site of inflammation in the lungs, stimulating the immune system to produce a stronger and longer-lasting response, reducing side effects and improving therapeutic efficacy. Genetically engineered nanomaterials can be precisely designed to target specific bacteria with less interference with other normal flora. The production process of novel nanomaterials is often complex and requires highly specialized equipment and skills, resulting in high production costs, which may limit their widespread clinical use. Although novel nanomaterials are designed and prepared with biocompatibility in mind, their long-term or large-scale use may still pose potential biological risks to the human body, such as cytotoxicity and immune reactions. Therefore, the application of novel nanomaterials is still in the research stage in the treatment of bacterial pneumonia, and their long-term effects and safety need to be further tested and verified.

## 5. Conclusions and outlook

Bacterial pneumonia is a serious infectious disease, and its current therapeutic strategies have led to the development of multi-drug resistant bacteria. Finding drugs that are alternatives to traditional antibiotics would be an effective solution to this challenge [133]. Currently, nanomedicines can change the size of the drug, and improve the targeting and penetration of antibiotics, thus improving bioavailability and reducing systemic toxic effects, as well as solving the problem of developing antibiotic resistance. The treatment of bacterial pneumonia through nanomedicine not only effectively sterilizes the bacteria and reduces the body's inflammatory response, but also regulates the body's immune function through immune response, preventing the occurrence of re-infection.

With the development of biomedicine, modern medicine has put forward the development direction of precision medicine, aiming to develop new methods and technologies for precision diagnosis and treatment. As emerging technologies in the field of chemistry, targeted degradation protein technology [134] and single-cell metabolomics [135] have gradually been noticed by researchers and have shown great advantages. Firstly, protein targeting technology is able to target specific proteins for precise detection and analysis. In the study of bacterial pneumonia, this technology can help identify specific proteins associated with bacterial pneumonia, thereby revealing the molecular mechanisms of disease onset and progression. For example, through protein-targeting technology, researchers can identify changes in the expression levels of certain proteins in patients with bacterial pneumonia, which may be related to factors such as inflammatory response, immune response or bacterial virulence [136]. Second, single-cell metabolomics technology is able to study changes in metabolites at the single-cell level, providing new perspectives for understanding metabolic abnormalities in bacterial pneumonia. Metabolomics is the science of studying changes in metabolites in living organisms, and single-cell metabolomics further refines the study to individual cells [137]. In bacterial pneumonia, there may be differences in the metabolic state of different cell types. And single-cell metabolomics techniques can reveal these differences, and help researchers under-

stand the impact of bacterial pneumonia on cellular metabolism. In conclusion, combined treatment of bacterial pneumonia with emerging technologies will be the future development direction, thus promoting the development of bacterial pneumonia to precision medicine.

From the clinical point, there is still a lot of work to be done to apply nanomedicines in the clinic. Firstly, basic research should be strengthened to thoroughly study the interaction mechanism between nanomedicines and bacterial pneumonia pathogens, so as to provide a theoretical basis for clinical application. Secondly, clinical trials should be carried out to verify the safety and effectiveness of nanomedicines in the treatment of bacterial pneumonia through rigorous clinical trials, to provide scientific basis for the promotion of application, and to optimize the design of nanomedicines to improve their targeting and bioavailability through the clinical needs. In conclusion, the development trend of nanomedicines in clinical treatment is positive, and the wider application of nanomedicines in the treatment of bacterial pneumonia can be promoted by strengthening basic research, conducting clinical trials, and optimizing drug design. Novel nanomedicines will bring new expectations to patients with bacterial pneumonia in the future.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Weiqian Jin:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation. **Lin Liao:** Writing – original draft, Methodology, Data curation. **Tao Qin:** Writing – review & editing, Visualization, Validation. **Xiaoxuan Guan:** Writing – original draft, Software, Investigation. **Huyang Gao:** Writing – review & editing, Investigation. **Peng Liang:** Resources, Investigation. **Ming Gao:** Writing – review & editing, Supervision, Funding acquisition. **Junyu Lu:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

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## Supplementary materials

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