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# Unraveling persistent bacteria: Formation, niches, and eradication strategies

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ABSTRACT

Persistent bacteria (persisters) are phenotypic variants that emerge either randomly or in response to a range of adverse environmental conditions. Persistence represents a state whereby a subpopulation of microorganisms can spontaneously enter a "dormant" state in response to environmental factors, while simultaneously exhibiting elevated tolerance to antimicrobial agents. This review provides the current definition of bacterial persistence and summarizes the mechanisms of persisters formation as well as the various niches of bacterial persistence encountered in clinical practice. Strategies targeting persisters are outlined, including but not limited to direct killing, awakening of persistent bacteria, combined clearance, and inhibition of persistence formation, and we conclude by proposing challenges and solutions for addressing bacterial persistence in current clinical practice.

## 1. Introduction

Bacterial infections have long stood as a primary threat to human health, with the discovery and translation of antibiotic agents in the last century being a major contributor to increased life expectancy. However, the widespread use of antibiotics has led to the emergence of many drug-tolerant bacteria and a looming global crisis. One of the key contributors to antibiotic treatment failure and the recurrence of infections is bacterial persistence (Fauvart et al., 2011; Kint et al., 2012). These surviving bacteria, termed persistent bacteria, are a particular subpopulation of bacteria that exhibit characteristics that make them distinct from the more commonly studied resistant bacteria. Upon entering a "dormant" state, persistent bacteria become refractory to antibiotic treatment, but may resume growth under favorable conditions, thus perpetuating recurrent bacterial infections (La Rosa et al., 2022; Michaux et al., 2022). Although studying persister bacteria is challenging, as outlined below, there is a widespread acknowledgement of the remarkable resilience exhibited by persistent bacteria, and that they present a formidable challenge for successful eradication.

There have been several review articles addressing the mechanism of persistent bacteria formation. For instance, Fisher et al. discuss the formation and regrowth mechanisms of persister in bacterial persistent infections (Fisher et al., 2017). Irving et al. review recent findings on the physiological roles of guanosine tetraphosphate and guanosine pentaphosphate ((pp)pGpp) in bacterial pathogenesis (Irving et al., 2021). Niu et al. provide a comprehensive update on the mechanisms of persisters formation (Niu et al., 2024). The formation of persistent bacteria is highly complex, resulting from a combination of multiple factors. Although existing reviews on the treatment of persisters have been summarized, they either cover extended periods without incorporating the latest research advancements, or lack a comprehensiveness overview of current treatment approaches for bacterial persisters. Moreover, the existing niches of bacterial persistence are rarely discussed, which significantly impacts the development and effectiveness of persister-targeted treatments. Given this context, the objective of this review is to provide the state of the art in our understanding of the biology of persistent bacteria, including mechanisms of formation and survival, as well as classification schemes introduced to aid definition. Furthermore, we will describe eradication strategies specifically targeting persistent bacteria, presented based on mechanism of action. These strategies encompass a range of approaches, including but not limited to direct killing, awakening of persistent bacteria, combination therapy, and inhibition of persistence formation. Through this systematic presentation of underlying biology and targeted strategies, we aim

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to identify future research directions that may in future provide improved treatment success for this highly relevant clinical problem.

## 2. Persistent bacteria

### 2.1. What are persistent bacteria?

Persistent bacteria are phenotypic variants that emerge either randomly or in response to a range of adverse environmental conditions within a bacterial population (Lewis, 2007; Fisher et al., 2017; Bollen et al., 2023). These bacteria can be classified into two types based on their origin. Environmentally triggered persistence is classified as Type I persistent bacteria, which primarily result from stressors such as nutrient limitation, antibiotic exposure, oxidative stress, and extreme pH (Helaine et al., 2014). In contrast, Type II persistent bacteria arise randomly. This type of persistence is less prevalent, comprising a smaller population that is frequently challenging to differentiate from type I persistent bacteria (Wang and Jin, 2022). Besides, it has been proposed that a hierarchy exists within the persister continuum, where some bacteria exhibit a high level of persistence, referred to as "deep persistence", while others display weaker persistence capacity, termed "shallow persistence" (Zhang, 2014; Pu et al., 2019). Notably, bacteria in a state of deep persistence may transition into the viable but non-culturable (VBNC) state under certain conditions. VBNC bacteria are unable to regrow on standard laboratory media that would otherwise support their proliferation. Instead, they require specific environmental triggers to revert to an antibiotic-sensitive, actively growing state (Lewis, 2007; Ayrapetyan et al., 2018; Kim et al., 2018a). Protein aggregation has been implicated in the transition between persistence and the VBNC state. Overexpression of ObgE has been shown to accelerate entry into persistence, whereas deletion of the *dnaK* gene promotes protein aggregation, reduces the number of persisters, and increases the proportion of VBNC bacteria (Dewachter et al., 2021; Bollen et al., 2025).

The fundamental characteristics of persistent bacteria have been well-established (Fisher et al., 2017; Balaban et al., 2019; Wainwright et al., 2021). (i) Persistent bacteria exist within the population at exceedingly low frequencies, typically comprising less than 0.1 % of the total population. (ii) Bacterial persistence arises in response to antibiotic or environmental stressors. (iii) Persistent bacteria are kept in a dormant state by adjusting carbon metabolism and energy changes, resulting in very slow and low-profile growth. (iv) They die much more slowly or are harder to eliminate at high antibiotic concentrations compared to non-persistent bacteria from the same population. Upon withdrawal of antibiotics, persistent bacteria can regrow and resensitized (Balaban et al., 2019; Wang and Jin, 2022). In addition to persistence, tolerance and resistance are distinct bacterial strategies that enable survival under antibiotic stress, each contributing to bacterial survival relative to susceptible strains. However, they differ significantly in their dynamics during antibiotic killing and in their population-level characteristics.

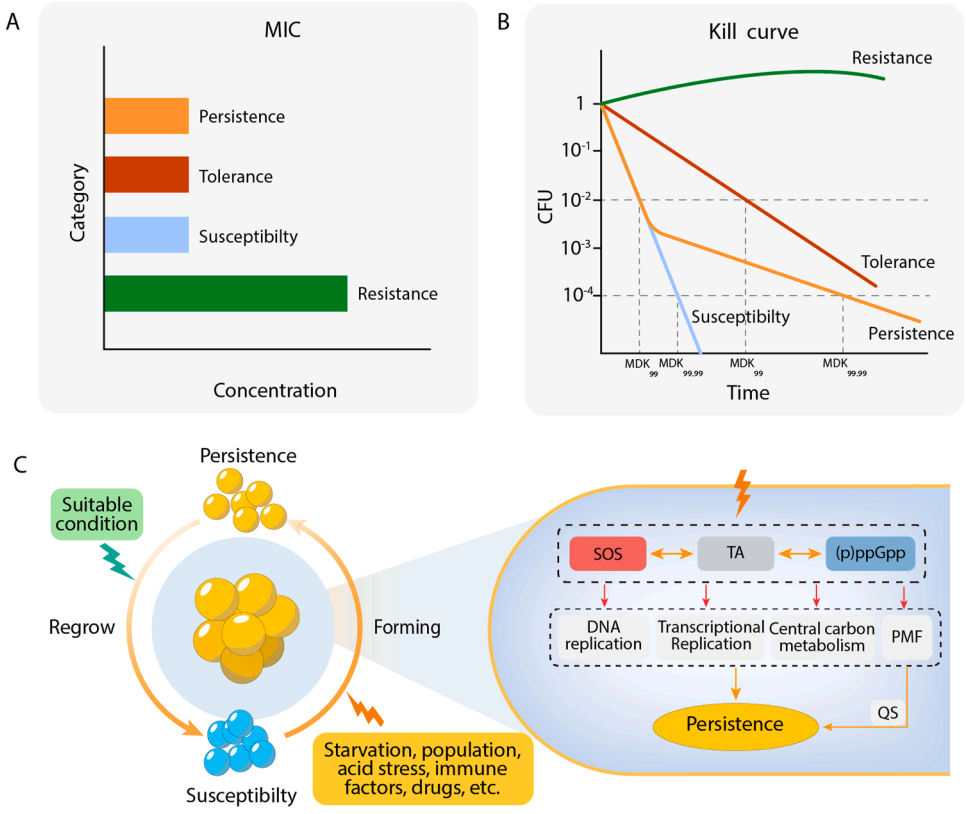


**Fig. 1. Key features of persister bacteria and comparison with tolerant and resistant equivalents.** (A) The theoretical time kill curves of bacterial populations, showing either an idealised pattern of susceptibility, persistence, resistance or tolerance in presence of bactericidal antibiotics. The susceptible bacteria die rapidly, while tolerant bacteria die more gradually. The resistant bacteria do not die but rather proliferate in presence of the antibiotics. The biphasic kill curve characteristic of persistence is due to the susceptible subpopulation dying quickly, while the persistent subpopulation dies more slowly. (CFU, colony forming units; $MDK_{99}$, minimum duration (time) required to kill 99 % of bacteria). (B) The difference between persistence, tolerance, susceptibility and resistance in relation to MIC. The MIC is only elevated for resistant bacteria, while it remains unchanged for all of the other categories. (C) The formation of persistent bacteria. Persistent bacteria can enter a persistent state after being stimulated by a certain stress, such as starvation, overpopulation, acid stress, immune factors or drugs. Should the environmental stress subside, the persistent bacteria can regrow (left). Highlighted on right, the mechanisms leading to persistance are shown. The SOS response, the toxin-antitoxin (TA) system and (pp)pGpp involved in the stringent response will be triggered by the stress factors. These subsequently lead to changes in DNA replication, transcriptions, metabolism and the proton motive force (PMF), which leads to the persistence phenotype.

Resistance arises from genetic mutations or acquisition of resistance genes, typically affecting the entire bacterial population. Resistant bacteria maintain active growth despite antibiotic presence and exhibit an elevated minimum inhibitory concentration (MIC) (Fig. 1A), with higher MIC values indicating stronger resistance (Brauner et al., 2016; Dewachter et al., 2019; Bollen et al., 2023). In contrast, persistence and tolerance exhibit phenotypic similarities and partially overlap, as both are characterized by no increase in the MIC. Tolerance is characterized by a uniform delay in killing across the bacterial population, leading to an extended minimum duration for killing 99 % of the bacteria ($MDK_{99}$) (Fig. 1B), while the bacteria ultimately die at a slower rate (Brauner et al., 2016; Levin-Reisman et al., 2019). However, persistence refers to a small subpopulation of phenotypically distinct, non-growing bacteria within an otherwise susceptible clonal population. These bacteria survive antibiotic treatment much longer than the majority of the population, prolonging $MDK_{99,99}$, while the initial killing phase ($MDK_{99}$) remains comparable to susceptible strains. This results in a biphasic killing curve (Fig. 1B), where the bulk population is rapidly eliminated, and a minor persister fraction survives in a dormant state (Levin-Reisman et al., 2019; Huemer et al., 2020; Eisenreich et al., 2022). Summarily, resistance and tolerance are characteristics of the entire bacterial population, whereas persistence refers to a small subpopulation within a clonal bacterial community that can survive antibiotic exposure (Balaban et al., 2019).

### 2.2. Formation of persistent bacteria

There are no clear-cut causes for the formation of persistent bacteria, but a number of mechanisms for their formation have been identified, and there are complex links between them (Fig. 1C). Toxin-antitoxin (TA) modules play a central regulatory role in persistent bacteria formation, inhibiting cellular processes such as translation (Germain et al., 2013; Winther et al., 2016), DNA metabolism (Harms et al., 2015), and the membrane potential (Dorr et al., 2010; Verstraeten et al., 2015). TA systems could be upregulated or activated by the accumulation of (pp)pGpp during the “stringent response” (Huemer et al., 2020), in which (pp)pGpp is synthesized during nutrient starvation and other stress responses such as fluctuations in oxygen, changes in pH, osmotic shock, and temperature variations. The stringent response modulates transcription in order to reduce growth and secure the bacterial survival (Hauryliuk et al., 2015; Harms et al., 2016). Another pathway is the SOS response (Harms et al., 2016). The SOS response is a conserved DNA repair and regulatory mechanism triggered by double-strand breaks during replication fork stalling, replication-transcription collisions, and transcriptional stalling, or DNA-damaging agents such as UV irradiation, antibiotics, oxidants, and high external pressure, leading to the generation of single-stranded DNA (ssDNA) (Baharoglu and Mazel, 2014; Zou et al., 2021). Additionally, quorum sensing (QS) is found to facilitate the formation of persistent bacteria (Fig. 1C) (Leung and Levesque, 2012; Maisonneuve and Gerdes, 2014; Amato and Brynildsen, 2015; Khan et al., 2020b; Personnic et al., 2023). Molecules such as indole and competence-stimulating peptide (CSP), acting as QS molecules, have demonstrated the ability to foster the development of persistent bacteria in *Streptococcus pneumoniae* (*S. pneumoniae*) (Gollan et al., 2019).

### 2.3. Niches of persistent bacteria

Persistent bacteria predominantly inhabit hostile environments, where they transition into a persistent state in response to environmental challenges. Accordingly, persistent bacteria can be found in different niches, such as liquid cultures (planktonic bacteria), biofilms, intracellular cavity, small community variants (SCVs), granuloma and abscesses (Proctor et al., 2014; Fisher et al., 2017; Peyrusson et al., 2020; Cronan, 2022; Masters et al., 2022; Choi et al., 2023).

#### 2.3.1. Liquid cultures (planktonic bacteria)

Persistent bacteria can be found in liquid cultures (planktonic bacteria) (Fig. 2A). Bacteria can enter persistence either spontaneously or in response to specific stimuli during their growth (Arnoldini et al., 2012). During the stationary phase, the primary stress encountered is nutrient limitation, which induces significant shifts in bacterial metabolism and gene expression patterns (Finkel, 2006; Lewis, 2007). Concurrently, the accumulation of metabolic byproducts such as organic acids leads to a decline in environmental pH, further impacting cellular stability and physiology (Sánchez-Clemente et al., 2018). As a result, the stationary phase typically harbors a higher proportion of persistent bacteria compared to the exponential growth phase. Enhanced quorum sensing (QS) activity during this phase may further contribute to the enrichment of persistent cells (Balaban et al., 2019; Mukherjee and Bassler, 2019; Verstraete et al., 2022; Wang and Jin, 2022). Nevertheless, it is important to note that both type I and type II persisters can be present at any given time within liquid cultures.

#### 2.3.2. Biofilm

Biofilms are considered to harbor bacteria displaying both tolerance and persistence (Lewis, 2007; Yan and Bassler, 2019; Choi et al., 2023) (Fig. 2B). Bacteria situated at the periphery of the biofilm benefit from abundant oxygen and nutrient availability, those residing deeper within confront nutrient scarcities and various stressors, which would trigger a response from the SOS as well as the (pp)pGpp and TA systems, facilitating bacterial entry into the persistent state (Orazi GO’Toole, 2019; Guo et al., 2022). Spoering et al. concluded that *P. aeruginosa* biofilms exhibit similar resistance to antibiotics and a biocide as stationary phase planktonic bacteria. Kline et al. emphasized that the mechanisms underpinning the ability of otherwise susceptible *S. aureus* to tolerate and survive antibiotic challenge may be essentially the same (Spoering and Lewis, 2001; Kline et al., 2016). Drescher et al. documented that significantly higher numbers of persistent bacteria in biofilms than planktonic stationary phase were found with high doses of antibiotics (Drescher et al., 2019). Owing to their dormant state and profound localization within biofilms, persistent bacteria elude detection and eradication, rendering biofilms a formidable impediment in bacterial infection eradication endeavors.

#### 2.3.3. Intracellular bacteria and small colony variants

Intracellular bacteria play important roles in the pathogenesis of diverse diseases and constitute essential elements of chronic, recurrent, and latent infections (Feng et al., 2022) (Fig. 2C). The intracellular milieu is hostile, characterized by low pH, abundant reactive enzymes, and oxidative stress. Intracellular bacteria will adjust their strategies to cope with these harsh environments. By employing fluorescent reporter genes to monitor individual growth rates, dormant bacteria have been detected within intracellular infections caused by *S. aureus* (Garzoni and Kelley, 2009; Peyrusson et al., 2020), *Salmonella* (Claudi et al., 2014), *Escherichia coli* (*E.coli*) (Helaine et al., 2019), *Mycobacterium tuberculosis* (*M. tuberculosis*) (Manina et al., 2015) and *Legionella cherrii* (*L. cherrii*) (Personnic et al., 2019), exhibiting notable antibiotic tolerance over extended durations (Wang et al., 2023). A recent finding indicates that a minor subset of intracellular bacteria undergoes a transition to a persistent state in response to environmental pressures imposed by host cells. *S. aureus* persisters have been observed intracellularly, and their metabolic activity is maintained accordingly by adjusting center carbon metabolism (Peyrusson et al., 2020).

Additionally, SCVs, as a classical type of intracellular bacteria that transition into a slow-growth state, manifest sluggish growth under nutrient-deficient and adverse conditions. SCVs are distinguished by the formation of diminutive colonies, reduced metabolic activity, slow proliferation and diminished ATP levels (Kahl, 2014; Nasser et al., 2020). SCVs and persistent bacteria commonly emerge from bacteria recuperating from intracellular environments or stress exposure. Similar to persisters, SCVs are capable of resuming growth post-stress cessation

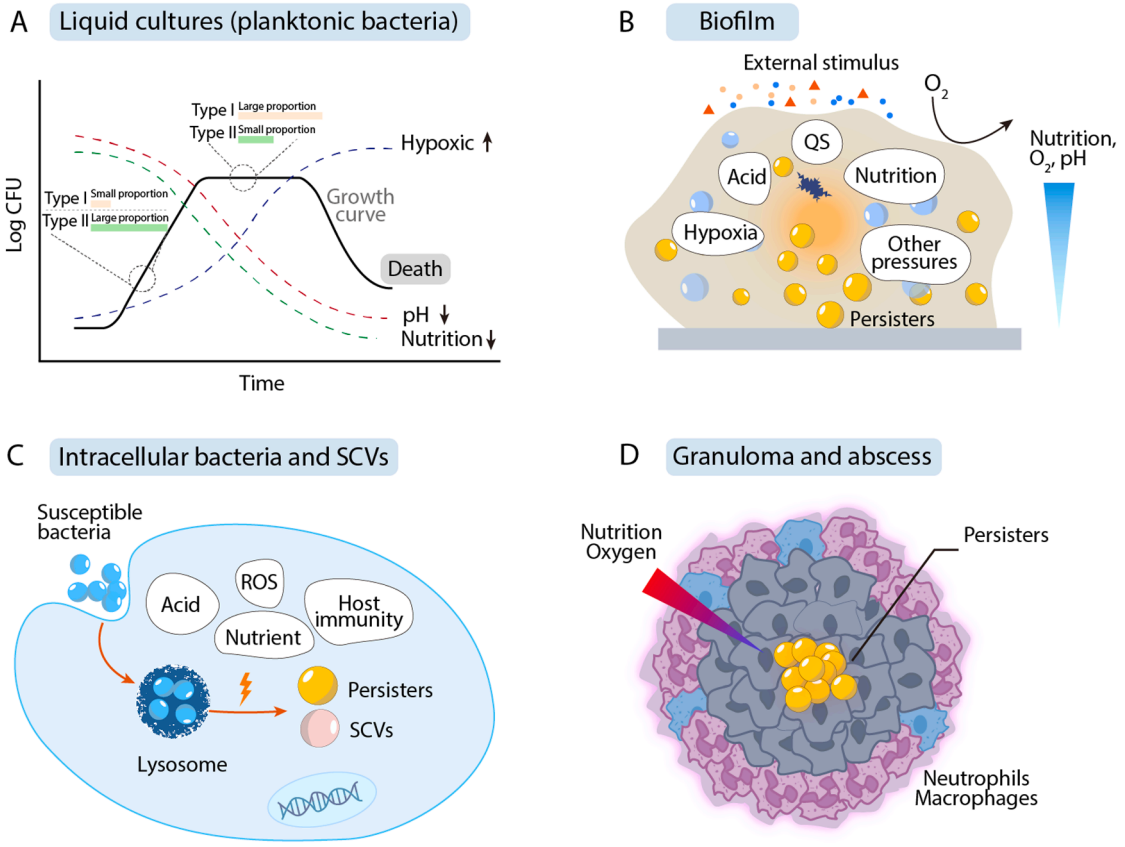


**Fig. 2. Niches of persistent bacteria. Persistent bacteria are induced in harsh environments that cause the bacteria to become dormant.** (A) Liquid cultures (planktonic bacteria). When bacterial growth, here measured in CFU over time, reaches a stable period in the stationary phase, it will face a large number of bacteria, low nutrition and various acidic anoxic environments, which will stimulate bacteria to enter a persistent state. (B) Biofilm. Biofilm interiors are typically hypoxic, low in pH, and nutrient poor, and present a complex microenvironment including persistent bacteria. (C) Intracellular persistent bacteria and SCVs. The presence of a large amount of dissolved oxygen, active enzymes, an acid environment and various organelles in the host cell will lead to a reduction of bacterial metabolism and induction of persistence. SCV is a subgroup of slow-growing bacteria that go dormant during the growth phase and under harsh conditions and the same dormant stress state as persistent bacteria under harsh conditions. (D) Granuloma and abscess. Bacteria in granulomas and abscesses are surrounded by immune cells in a largely nutrient-poor and anaerobic state, and are surrounded by immune cells in an intricate microenvironment that imposes a variety of environmental constraints on bacterial growth, promotes bacterial dormancy, and favors the emergence of persistent bacteria.

(Helaine et al., 2014; Loss et al., 2019; Zhou et al., 2022). Investigations have underscored numerous metabolic resemblances between SCVs and persistent bacteria. It is likely that persistent bacteria are indeed present in SCVs, or alternatively, viewed from another standpoint, persistent bacteria may coexist within SCVs as a distinct subset (Vulin et al., 2018), but this idea needs more research and validation (Proctor et al., 2014).

*2.3.4. Granuloma and abscess*

Granuloma is a focal aggregate of immune cells that forms in response to an inflammatory stimulus, such as an infectious pathogen or a foreign body (Gengenbacher and Kaufmann, 2012; Nathan, 2016). Numerous necrotic cells are present around the granuloma and there is a concentration of bacteria there (Cronan, 2022). In contrast, *S. aureus* abscess communities (SAC) are the result of bacteria acting on immune cells, prompting them to gather to form a natural barrier in which the bacteria encapsulate themselves, enabling them to survive for long periods of time within the soft tissues. Although the two niches by different mechanisms, the layer of mostly necrotic host immune cells unintentionally creates an additional protective barrier that prevents newly recruited host immune cells from penetrating the abscess and killing the bacteria (Fig. 2D). Under the continuous influence of host and environmental pressures, bacteria within SAC and granulomas face scarcity in both nutrients and oxygen, creating an environment conducive to their persistence rather than active replication (Cronan, 2022; Masters et al., 2022). To survive in SAC and granulomas, entry into a persistence become strategies for bacterial survival, making the formation of persistent bacteria in this environment (Cheng et al., 2009; Garzoni and Kelley, 2009; Gengenbacher and Kaufmann, 2012).

## 3. Strategies for removing persistent bacteria

Currently, the eradication of persistent bacteria can generally be divided into three broad strategies (Fig. 3). (i) Direct killing of persistent bacteria. This approach involves the use of novel-generation antibiotics and antimicrobial peptides (AMPs) as primary antibacterial agents. Additionally, other antimicrobial agents have been developed, which we refer to as “other antimicrobials”, including bactericidal agents that are neither antibiotics nor AMPs. In addition to these agents, other antimicrobial strategies, such as metals, phages, photothermal therapy (PTT), photodynamic therapy (PDT), nitric oxide (NO) treatment and weak electrochemical currents are also capable of directly killing persistent bacteria. (ii) Drug combinations. These strategies encompass the use of traditional antibiotics in combination with other antibiotics or with non-antibiotic agents. In the case of combinations involving antibiotics and nonantibiotics, nonantibiotics may be utilized, for example, to awaken or sensitize persistent bacteria, subsequently enhancing the efficacy of the antibiotic. (iii) Inhibition of persistent bacteria formation. This strategy aims to reduce or inhibit the formation of persistent bacteria through pathway interference. This may be achieved by blocking bacterial communication or inhibiting pathways such as TA systems and

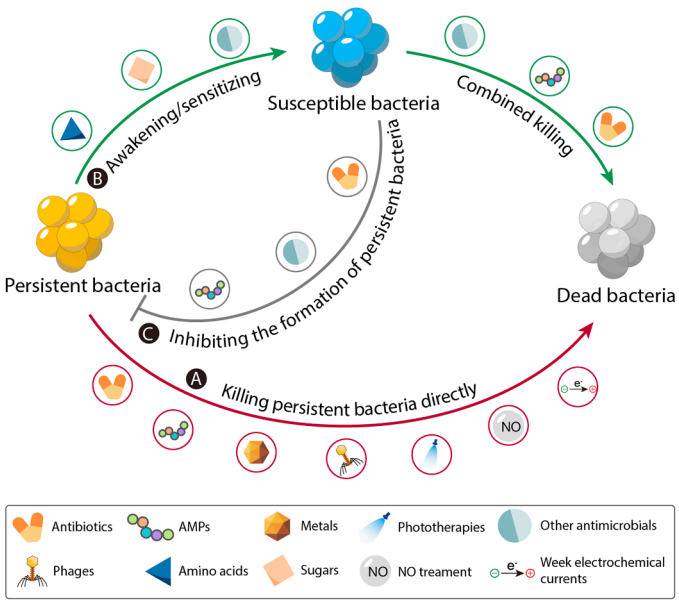


**Fig. 3. Three antimicrobial strategies targeting persistent bacteria.** (A) Direct killing of persistent bacteria. This approach involves the use of novel-generation antibiotics, AMPs, other antimicrobial agents, metals, phages, phototherapies, NO treatment and weak electrochemical currents. (B) Drug combinations. These strategies use combinations of conventional antibiotics and/or nonantibiotics agents to sensitize persisters, followed by killing them. (C) Inhibiting the formation of persistent bacteria. These strategies aim to prevent the emergence of persisters by blocking bacterial communication or inhibiting pathways such as TA and (pp)pGpp.

(pp)pGpp, which are involved in persister formation. These strategies are not necessarily strictly independent, and it is possible that multiple mechanisms can be combined.

### 3.1. Killing persistent bacteria directly

Direct killing of persistent bacteria requires rapid and intense damage on the bacterial components such as cell wall, membrane, nucleic acid and proteins etc. (Liu et al., 2023) (Fig. 4).

#### 3.1.1. Novel-generation antibiotics and other antimicrobials

Targeting the bacterial cell membrane is an effective strategy, as it not only disrupts the membrane directly but also alters its permeability, facilitating the enhanced uptake of other drugs. Antibiotics like polymyxin B and colistin, for example, target the negatively charged lipopolysaccharides and phospholipids on the cytoplasmic membrane, causing membrane disruption and lysis in persistent bacteria (Cui et al., 2016; Mohiuddin et al., 2020; Sabnis et al., 2021). Some novel small-molecule antimicrobials, such as the phenethylamine derivative SPI009 (Liebens et al., 2017), peroxisome proliferator-activated receptor gamma activator nTZDpa (Kim et al., 2018b), aryl-alkyl-lysines structural compound NCK-10 (Ghosh et al., 2016), retinoic acid analogs CD437 and CD1530 (Kim et al., 2018c), and the potent indigoid NPIMA (Song et al., 2019), disrupt the phospholipid bilayer and exert a strong osmotic effect that kills persistent bacteria. The nitrofuran IITR06144 enhances the bactericidal activity of aminoglycosides by disrupting membrane permeability and inducing DNA damage (Bhando et al., 2020). Mitomycin C (Kwan et al., 2015) and cisplatin (Chowdhury et al., 2016) have been shown to induce DNA crosslinking, leading to the eradication of persistent bacteria.

The natural product aureomycin A (ChryA) competitively inhibits GlmU and DapD enzymes, targeting the synthesis of cell wall peptidoglycan precursors and lysine in *S. aureus* persisters (Jia et al., 2023). Additionally, several natural extracts have shown potential in targeting recalcitrant bacteria, though their mechanisms still require further exploration. For example, two natural compounds, 4,6-dibromo-2-(2′, 4′-dibromophenoxy) phenol and 3,4,6-tribromo-2-(2′,4′-dibromophenoxy) phenol demonstrate bactericidal effects against Methicillin-resistant *S. aureus* (MRSA) and *P. aeruginosa* persistent bacteria (van Geelen et al., 2020). Squalamine exhibits the ability to eradicate persistent and VBNC bacteria of *Acinetobacter baumannii* (*A. baumannii*) (Nicol et al., 2019).

#### 3.1.2. AMPs (antimicrobial peptides)

AMPs are small proteins with potent antibacterial, antiviral, and antifungal activity (Lazzaro et al., 2020). AMPs exhibit good scavenging ability against persistent bacteria. 2D-24 is a dendrimeric peptide composed of varying numbers of arginine and tryptophan residues. This peptide effectively targets persistent bacteria by disrupting bacterial membranes and potentiating the activity of antibiotics such as ciprofloxacin, tetracycline, and carbenicillin (Bahar et al., 2015b). Similarly, a penetrating peptide containing different arginine and tryptophan in the AMP framework based on the 1,3,5-triazine structure, along with its derivative TN-5, has proven effective in eliminating persistent *E. coli* (Chen et al., 2011; Bahar et al., 2015a). Additionally, the lysine-containing AMP ZY4, reported by Mwangi *et al.,* demonstrates bactericidal activity against biofilms and persistent *A. baumannii* by permeabilizing bacterial membranes (Mwangi et al., 2019). An imidazole-cation AMP has been designed for the targeted removal of persistent MRSA and biofilm (Basak et al., 2017). Liu et al. developed various host defense peptides and peptide-like polymers, utilizing ring-opening polymerization, for the effective removal of persistent MRSA (Zhou et al., 2020; Xie et al., 2021).

The acyldepsipeptide ADEP4 activates bacterial caseinolytic peptidase P (ClpP), resulting in nonspecific protease activity that targets over 400 of intracellular proteins, thereby killing persistent bacteria. When combined with gentamicin, it demonstrates potent activity against persistent bacteria, making it an effective agent for eradicating persistent bacterial infections (Conlon et al., 2013). Lassomycin is a cyclic peptide synthesized via ribosomal pathways that exhibits activity against persistent *M. tuberculosis* by targeting the ATP-dependent protease ClpC1P1P2 (Gavrish et al., 2014). Furthermore, a sequence-specific pentamer, known as TM5, inhibits cytokine production induced by Gram-negative bacterial lipopolysaccharides, demonstrating efficacy against planktonic persistent bacteria and exerting bactericidal effects on biofilms formed by both Gram-negative and Gram-positive bacteria (Lin et al., 2022).

Direct conjugation of commonly used antibiotics with antimicrobial peptides has emerged as a promising strategy in drug development. For instance, Mohamed et al. (2017) synthesized a kanamycin-peptide conjugate (P14KanS) by coupling kanamycin with an antimicrobial peptide (P14LRR). Mechanistic studies revealed that P14KanS exerts its antimicrobial action through selective disruption of the bacterial membrane (2017). Similarly, conjugates of vancomycin with innate defense regulator (V-IDR1018) (Etayash et al., 2021) and vancomycin-D-arginine (V-r8) (Antonoplis et al., 2018) have been developed to clear biofilms of MRSA and persistent bacteria, respectively, by inducing cytokine production and enhancing transporter activity. These conjugates exhibit higher clearance efficiency compared to vancomycin alone.

#### 3.1.3. Phage

One of the key advantages of phage therapy over broad-spectrum antibiotics is its high specificity for target bacterial pathogens, without causing adverse effects on the host or its symbiotic microbiota, thereby minimizing secondary impacts (Sarker et al., 2016). Phages exert their bactericidal action by ultimately lysing bacteria (Pacios et al., 2020). Phage-derived enzymes, such as Art-175 (Briers et al., 2014), LysH5 (Gutierrez et al., 2014), CF-301(Schuch et al., 2013) CHAP(K) (Fenton et al., 2013), and PlyC (Shen et al., 2013) have demonstrated

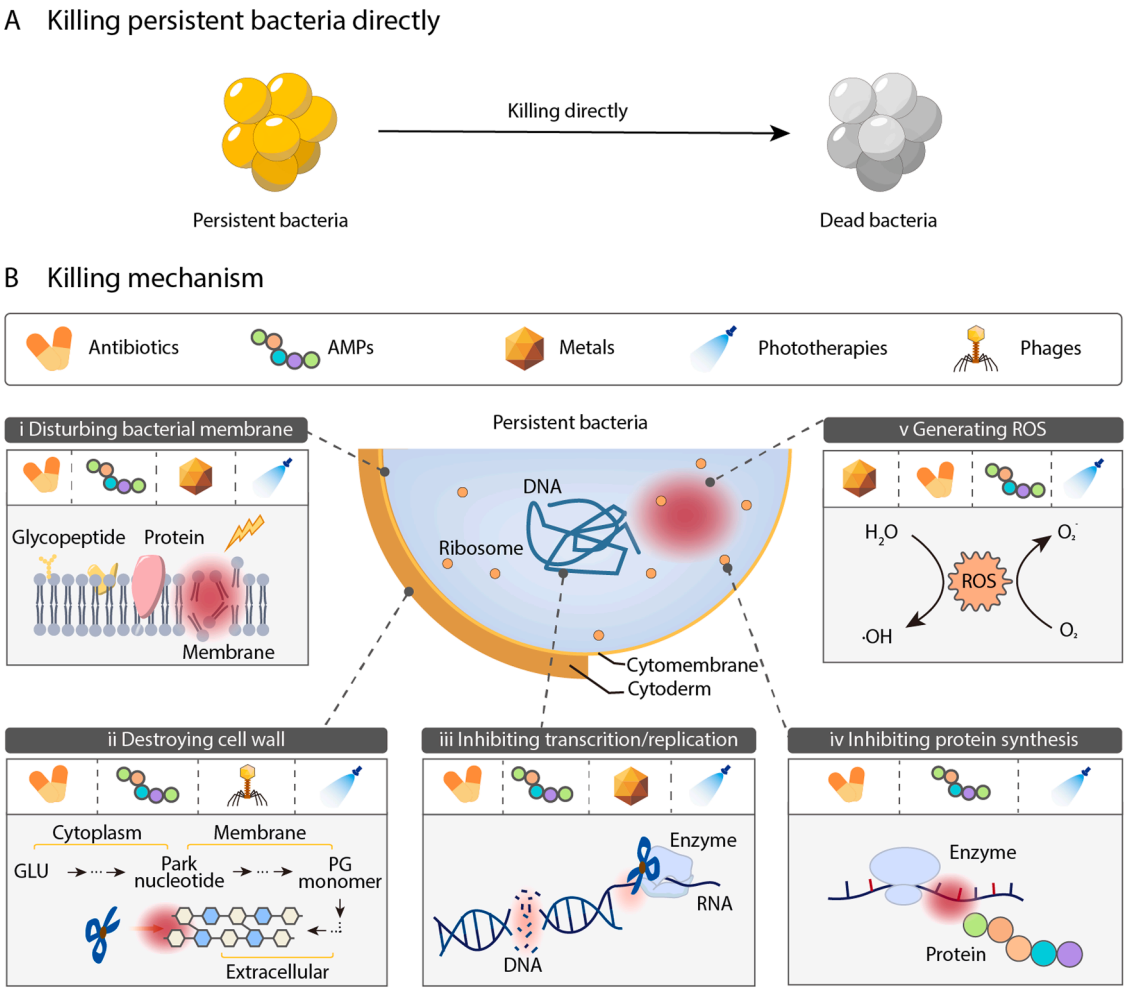


**Fig. 4. Strategies for direct removal of persistent bacteria.** (A) Schematic diagram illustrating the direct killing of persistent bacteria. (B) Classification by mechanism of action. These mechanisms listed may not be mutually exclusive, and multiple mechanisms could be combined. (i) Disturbing bacterial membrane. (ii) Destroying cell wall. (iii) Inhibiting transcription/replication. (iv) Inhibiting protein synthesis. (v) Generating ROS.

effectiveness in inhibiting and killing persistent *S. aureus*, along with potent anti-biofilm activity. The *S. aureus*-specific phage Sb-1 can degrade the MRSA polysaccharide matrix and target persistent bacteria, making it suitable for treating biofilm-related infections (Tkhilaishvili et al., 2018). Recently, phage-antibiotic combination therapy has been proposed as a strategy to eradicate persistent bacteria and eliminate biofilms on medical devices, prosthetic joints, etc. (Kebriaei et al., 2020; Fedorov et al., 2023; Osman et al., 2023). For example, Paride, a newly isolated *P. aeruginosa* phage, can directly replicate and induce lysis of persisters. When combined with meropenem, Paride can eradicate persistent bacteria in vitro and reduce bacterial infection in mouse tissue (Maffei et al., 2024), demonstrating strong targeting and scavenging capabilities.

### 3.1.4. Metals

Metals offer a promising strategy against bacteria, including biofilms and persisters by directly damaging membrane surfaces, altering membrane permeability, and disrupting DNA and iron metabolism (Basavegowda and Baek, 2021; Han et al., 2022). Copper enhances the killing of persistent bacteria under anaerobic conditions by disrupting proteins involved in bacterial respiration. The primary cause of copper toxicity is the disruption of Fe-S protein clusters, an oxygen-independent process (Moreira Martins et al., 2020). Magnesium hydroxide nanoparticles, due to their small size, significantly kill persistent *E.coli* (Nakamura et al., 2021).Caffeine-coated gold nanoparticles exhibit multifaceted characteristics, including the ability to inhibit biofilm formation, disperse mature biofilms, and eradicate *S. aureus*, *L. monocytogene, P. aeruginosa* and *E. coli* persisters (Khan et al., 2021). Gold nanoclusters coated with adenosine triphosphate (AuNC@ATP) kill persistent bacteria by exploiting their low metabolic activity and increasing membrane permeability (Bekale et al., 2023).

### 3.1.5. Other direct killing strategies

Emerging physical strategies, including phototherapies (PDT and PTT), NO treatment and week electrochemical currents, show considerable promise in eradicating persistent bacteria. In PTT therapy, blue light has been shown to disrupt proton flux across the inner membrane, thereby affecting the viability of persistent *E.coli* (Abana et al., 2017). Simultaneously, Xu et al. developed a novel multimodal antibacterial platform integrating both PDT and PTT, which not only eradicates pathogenic bacteria but also visualize ROS generation and promotes wound healing (He et al., 2024b). The NO treatment strategy effectively targets Type I persistent bacteria during the stationary phase by reducing protein and RNA degradation in these persisters (Orman and Brynildsen, 2016). Week electrochemical currents have been shown to reduce persistent bacteria by increasing ROS production, although the exact mechanisms require further investigation (Niepa et al., 2012; Schmidt-Malan et al., 2015; Voegele et al., 2015). Similarly, sonodynamic and magnetic therapies (Cheeseman et al., 2020; Wu et al., 2023; He et al., 2024a), currently under development, offer precise and efficient alternatives, further expanding the growing arsenal of advanced modalities for tackling persistent bacterial infections.

### 3.2. Drug combination

Persistent bacteria pose a significant challenge to the effectiveness of single antibiotics, which is why strategies for combined clearance of persistent bacteria through multiple routes have emerged. These strategies include the combinations of antibiotics and nonantibiotics, as well as combinations of conventional antibiotics. Such approaches involve multiple mechanisms of action, which may include the use of an auxiliary agent that lacks intrinsic antimicrobial activity but enhances antibiotic efficacy, or the combination of multiple antibiotics with synergistic modes of action. A key consideration when employing combination strategies is whether they lead to beneficial synergistic effects or potential antagonistic effects that could undermine the efficacy of the antibiotics. Harnessing the synergistic potential of these combinations is crucial for achieving potent eradication of persistent bacteria. Furthermore, combining different treatments can also help reduce the development of antibiotic resistance (Fig. 5A).

#### 3.2.1. Combinations of conventional antibiotics

Combining multiple antibiotics provides an effective approach for eliminating persistent bacteria (Chung and Ko, 2019). The available antibiotics target various cellular components, including but not limited to: disrupting cell wall integrity (e.g., β-lactams and glycopeptides), disrupting the cell membrane (lipopeptides), inhibiting protein synthesis (chloramphenicol, macrolides, tetracyclines), blocking transcription (rifampicin), and impeding DNA synthesis (fluoroquinolones) (131) (Fig. 5B).

Doxycycline, combined with daptomycin or ceftriaxone, demonstrates efficacy in treating persistent *Borrelia burgdorferi* (*B. burgdorferi*) bacteria in Lyme disease (Defraine et al., 2018). Similarly, daptomycin combined with tobramycin (Lechner et al., 2012) or gentamicin (Baltch et al., 2008) shows killing efficacy against *S. aureus* persisters. Another example includes tobramycin combined with colistin or ciprofloxacin, which can eradicate persistent bacteria during both exponential and stationary phases of *A. baumannii* growth. Down-regulation of genes encoding universal stress proteins and efflux pumps in response to tobramycin and colistin reduces antibiotic efflux, thereby enhancing bacterial clearance (Kashyap et al., 2021). Colistin increases membrane permeability, promotes ROS production, and facilitates the entry of antibiotics, such as amikacin (Chung and Ko, 2019), tobramycin (Kashyap et al., 2021) gentamicin (Cui et al., 2016; Zheng et al., 2020) and ofloxacin (Cui et al., 2016; Zheng et al., 2020). Combining phenothiazines with ofloxacin disrupts persistent bacteria by inhibiting energy metabolism and proton gradient maintenance (Mohiuddin et al., 2022).

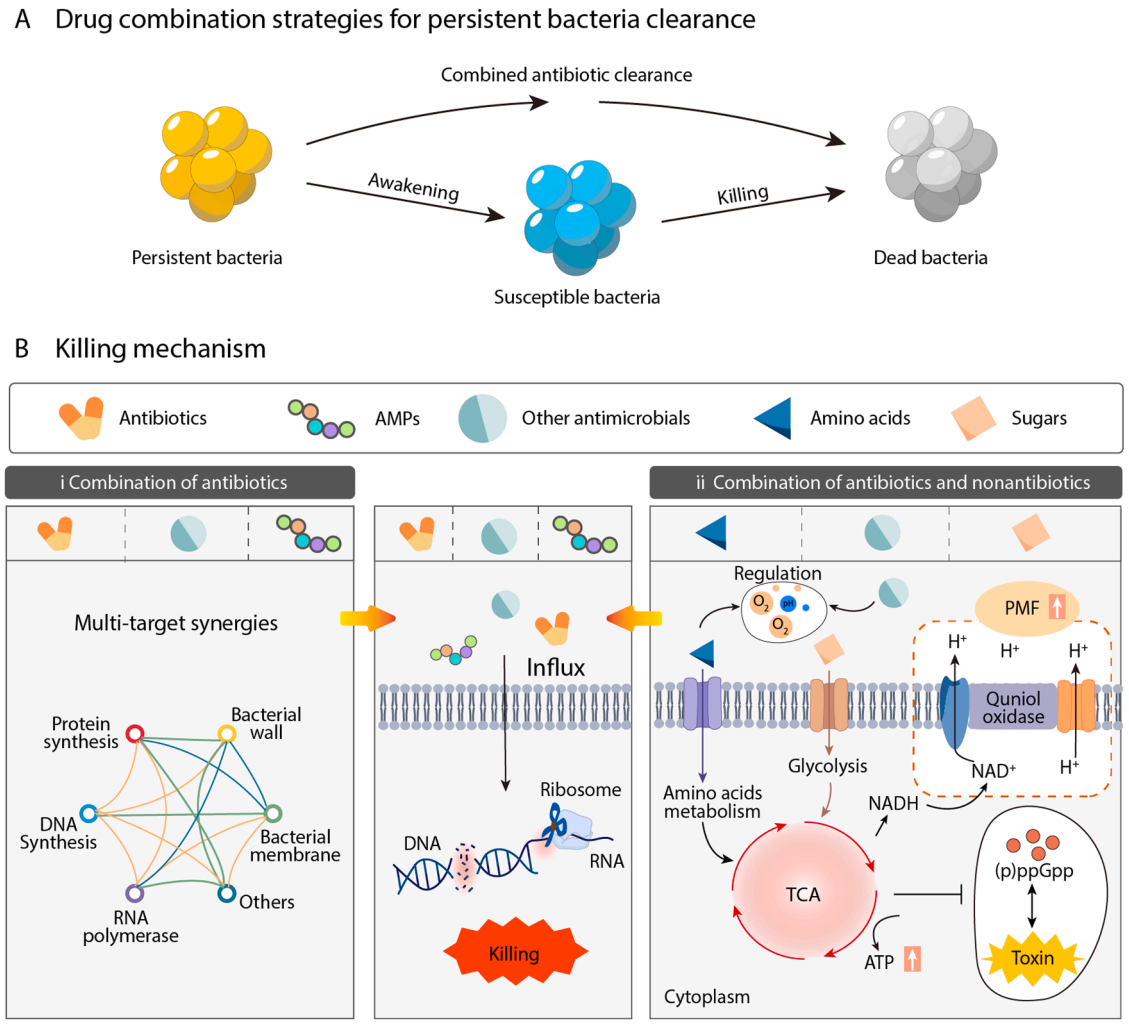


**Fig. 5. Drug combination strategies for persistent bacteria clearance.** (A) Schematic diagram of drug combination. (B) Killing mechanism. (i) Combination of antibiotics. Multi-antibiotic combinations can achieve persistent bacteria clearance by targeting different bacterial structures and mechanisms of action. Their synergistic effects significantly enhance the eradication of persisters. (ii) Combination of antibiotics and nonantibiotics. Removing environmental stress by increasing nutrient supply, raising oxygen levels or optimizing pH *etc*. can 'awaken' persistent bacteria. This awakening reverse persistence by adjusting the levels of (pp)pGpp and TA systems, reactivating bacterial metabolism, etc., thereby making them more susceptible to treatments. Consequently, drug combination strategies kill persistent bacteria by different mechanisms of action.

#### 3.2.2. Combinations of antibiotics and nonantibiotics

Nonantibiotics that modify the metabolism of persistent bacteria, such as altering glycolysis, boosting the tricarboxylic acid cycle (TCA), and up-regulating various other pathways (e.g., ROS and reactive nitrogen species), are used as adjuncts to enhance antibiotic killing. These nonantibiotics include amino acids, sugars and other metabolites. Additionally, nonantibiotics that alter the external environment can promote the awakening of persistent bacteria. These agents strengthen the bacterial PMF, facilitate antibiotic internalization, and enhance bacterial susceptibility to antibiotics (Meylan et al., 2017; Su et al., 2018; Liu et al., 2020a; MacLean et al., 2023) (Fig. 5B).

For instance, combining sugars such as mannitol, fructose, and glucose with the aminoglycoside kanamycin, significantly reduces *E. coli* and *S. aureus* persisters by altering bacterial metabolism, increasing PMF, and enhancing aminoglycosides uptake (Allison et al., 2011). The combination of the antibiotic-antimicrobial peptide Nisin was effective in reducing the formation of *Listeria monocytogenes* (*L. monocytogenes*) persistent (Narimisa et al., 2021), while combining Nisin with ampicillin successfully killed *Salmonella* persisters under mannose conditions (Rishi et al., 2018). Amino acids, similar to sugars, also regulate bacterial metabolism (Verstraete et al., 2022). Proline has been reported to reawaken persistent *P. aeruginosa*, while exogenous alanine can promote the resensitization of *E. coli* to kanamycin (Peng et al., 2015; Zhang et al., 2019). Exposure to acidic pH triggers persistence, but the addition of basic amino acids, such as L-arginine, enhances PMF and sensitizes bacteria to kanamycin by modifying the membrane pH gradient (Lebeaux et al., 2014; Verstraete et al., 2022). Similarly, L-serine (Duan et al., 2016), L-alanine, and cysteine (Liu et al., 2020b; Yamasaki et al., 2020; Zhen et al., 2020) enhance the efficacy of fluoroquinolones against *E. coli* and *M. tuberculosis* by boosting endogenous ROS production. In addition, exogenous adenosine can synergize with antibiotics by altering nucleotide metabolic pathways and reducing (pp)pGpp accumulation, as well as promoting ATP synthesis to reverse bacterial persistence (Kitzenberg et al., 2022; Li et al., 2023).

Beyond metabolism enhancement via metabolites, single chemical compounds like C10 (Kim et al., 2011) and the fatty acid signaling molecule cis-2-decenoic acid(Marques et al., 2014) have been shown to transition persistent *P. aeruginosa* and *E. coli* from a dormant state to a metabolically active state. The combination of nTZDpa and aminoglycosides effectively kills persistent bacteria, while dimercaptan combined with gentamicin eradicates *S. aureus in vitro* and significantly reducing bacterial load in a mouse model of chronic MRSA infection (Kim et al., 2019). Additionally, Zhao et al. suggested that freezing techniques enhance aminoglycoside uptake through the mechanosensitive ion channel MscL, independent of PMF (Zhao et al., 2020). Similarly, hypoionic shock also mediated by mechanosensitive ion channels, facilitates aminoglycoside influx to eliminate persistent bacteria (Jiafeng et al., 2015).

In addition, drug delivery systems (DDSs) enable precise delivery of antibiotics, increasing antibiotic internalization and altering the external environment of the bacteria, thereby enhancing antibiotic efficacy in removing persistent bacteria (Ashique et al., 2021; Cai et al., 2022). For example, a maltohexaose-modified catalase-gallium nanosystem awakens dormant *P. aeruginosa* biofilms by reconciling the oxygen gradient, boosting metabolism, and increasing nutritional iron demand (Jian He a, 2024). Gold nanoparticles with NO photothermal release also exhibit synergistic biofilm-clearing ability (Tang et al., 2021). Additionally, gluconic acid-chitosan nanoparticles show antibacterial activity against persistent bacteria and biofilms (Khan et al., 2020a), while poly(amino acid)-based nanoparticles specifically target dormant intracellular bacteria, offering a novel approach for intracellular bacterial elimination (Feng et al., 2022)

### 3.3. Inhibiting the formation of persistent bacteria

The formation of persistent bacteria is regulated by various signals, and inhibiting their generation by disrupting specific pathways has become a viable strategy. Approaches such as blocking QS, inhibiting the expression of (pp)pGpp, and targeting toxin-antitoxin (TA) systems have been developed (Fig. 6).

Relacin, a novel antibacterial agent, inhibits (pp)pGpp synthesis mediated by *RelA*, disrupting the transition of several Gram-positive bacteria into a stable growth state and leading to bacterial death, thus inhibiting the generation of persistent bacteria (Wexselblatt et al., 2012). TA systems play a central role in persistence, making them attractive drug targets. Inhibiting toxins can prevent growth arrest, while promoting their activity may drive persisters out of dormancy. For example, HipA, the first identified toxin linked to *E. coli* persistence, can be inhibited by compounds identified through structure-based virtual screening, significantly reducing persistence (Li et al., 2016). The Lon protease activates the TA system by degrading antitoxins. Inhibition of Lon protease activity can prevent toxin release, thereby blocking TA system-mediated entry of bacteria into the persister state (Harms et al., 2016; Michiels et al., 2016). Diosmin and nafcillin have been identified as potential inhibitors of Lon protease, capable of effectively downgrading the expression of type II TA system genes, thus preventing the formation of persisters (Narimisa et al., 2024). Similarly, the mazEF TA system is crucial for persistence; its overexpression induces persister formation, but direct interaction with rifampicin can inhibit this process (Alexander et al., 2020). In addition，disrupting folate metabolism can inhibit the generation of persistent bacteria (Morgan et al., 2018).

Bacteria are not isolated entities; they communicate via QS signaling molecules, making QS pathways effective targets for combating persistent bacteria in biofilms (Moker et al., 2010; Leung and Levesque, 2012). Strategies include degrading QS signaling molecules, inhibiting their production pathways, blocking receptor interactions, disrupting membrane transport, or capturing signaling molecules (Khan et al., 2020b). For example, BF8 is a QS inhibitor of *E. coli*, which can sensitize bacteria to ofloxacin by disrupting connections between biofilms if added exogenously(Pan et al., 2013). Similarly, QS-regulated phenol-soluble modulins decrease persistent bacteria number in *S. aureus* (Bojer, 2018).

## 4. Concluding remarks

In this review, we provided the current definition of bacterial persistence and summarized the mechanisms behind persisters formation, as well as the various niches of bacterial persistence encountered in clinical practice. We have also outlined comprehensively strategies for eradicating persister bacteria, including direct killing via novel-generation antibiotics, AMPs, other antimicrobial agents and strategies, drug combinations of conventional antibiotics and/or non-antibiotics, and inhibition of persister formation. These insights contribute to a broader understanding of persister formation and elimination, facilitating a deeper comprehension of their underlying mechanisms and potential therapeutic strategies.

However, many unresolved questions regarding the development and management of persister bacteria remain, highlighting the need for further investigation.

First, there is a lack of effective detection methods and treatment evaluations for persistent bacteria in infected tissues. Persistent bacteria often exist in traces across various tissue types and depths, making on-site, trace-level detection challenging. This gap significantly hampers the ability to assess drug efficacy and monitor patient recovery. Additionally, although several in vitro antibiotic induction models have been developed, their use has been controversial due to the considerable variability in the metabolic responses of persistent bacteria induced by different antibiotics. Constructing *in vivo* models of persistent bacterial infections is complicated by factors such as the deep penetration of persisters, the host microenvironment and immune response. Establishing reliable mechanisms for the induction, detection, and evaluation of persistent bacteria will be critical in advancing efforts to eradicate bacterial infections.

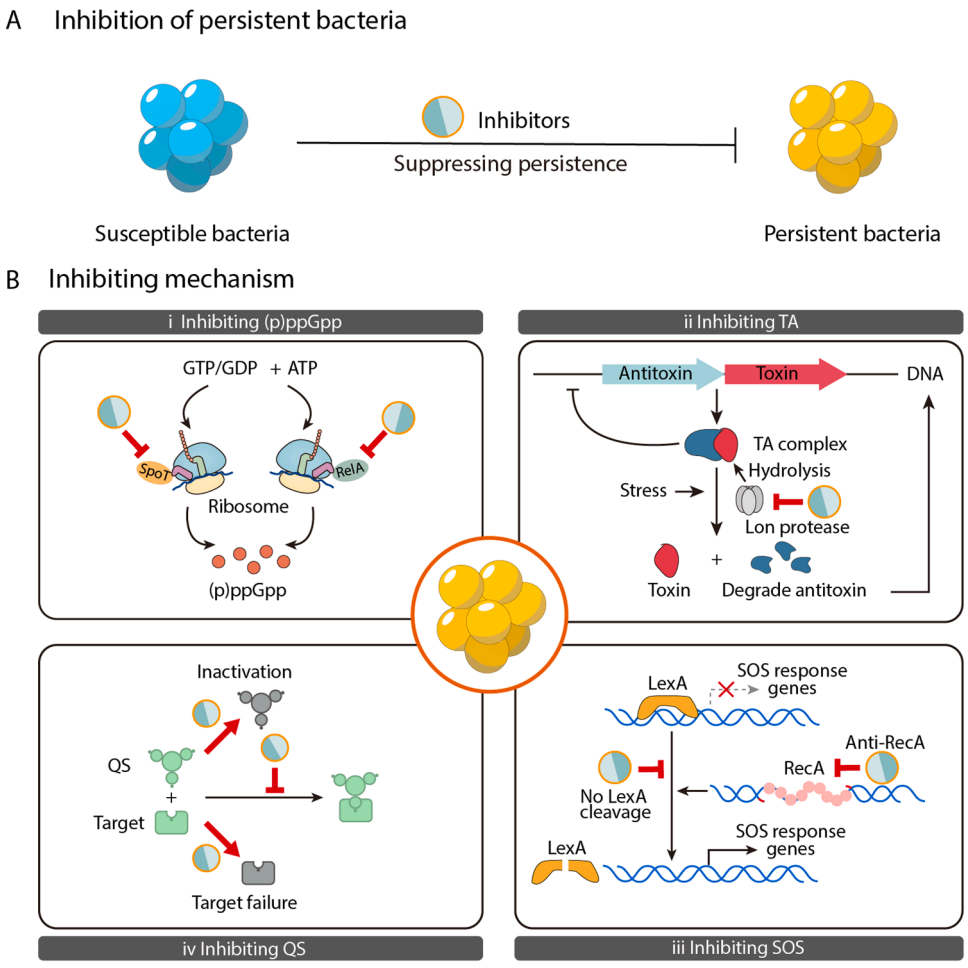


**Fig. 6. Inhibition of persistent bacteria.** (A) Schematic diagram illustrating the inhibition of persistent bacteria formation. (B) Inhibiting mechanisms. Cutting off one or more of these pathways before the formation of persistent bacteria. (i) Inhibiting (p)ppGpp. Blocking SpoT and RelA to inhibit the synthesis of (pp)pGpp. (ii) Inhibiting TA. Inhibiting the proteolysis of antitoxins by the Lon protease to prevent toxin release and TA system activation, thereby blocking TA signaling. (iii) Inhibiting SOS. Blocking the SOS response by regulating RecA and LexA, thus cutting off the link to the TA. (iv) Inhibiting QS. Disrupting QS signals to prevent inter-bacterial communication.

Second, the effect of the persister niches on drug efficacy has been overlooked. As mentioned above, persistent bacteria typically reside in deep tissues within a complex microenvironment, requiring drugs to penetrate tissue barriers and reach bacterial loci. This presents a significant challenge for bactericidal efficacy, as the ability of a drug may vary substantially when treating persisters in different niches. Furthermore, the microenvironment strongly influences the state of persistent bacteria. For example, hypoxic conditions may shift persistent bacteria from aerobic respiration to fermentation, which may drastically alter their susceptibility to different drugs. These factors highlight the need for further research on the impact of persister niches on the effectiveness of therapies targeting persister bacteria.

## CRediT authorship contribution statement

**Wang Xing:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Moriarty T. Fintan:** Writing – review & editing, Conceptualization. **Li Guofeng:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Huang Diandian:** Writing – original draft. **Kuhn Elian M.A:** Writing – original draft. **Yin Zibo:** Writing – original draft, Visualization, Conceptualization.

## Declaration of Competing Interest

The authors declare no competing interests.

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## Data availability

No data was used for the research described in the article.

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