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# Are bacterial persister cells really the cause of infection relapse/recalcitrance?

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**A B S T R A C T**

**Introduction**: Looking into the literature, many articles accuse bacterial persister cells as important causes of infection relapse/recalcitrance. This opinion paper, highlights the knowledge gaps and scientific misconceptions in experimental procedures regarding the role of persisters in relapse/recalcitrance of infections and recommends a roadmap for investigations in this field.

**Conclusion:** It is debated in this paper, that unless the queries and missing points are addressed clearly, persisters cannot be stigmatized as the culprit of infection relapse/recalcitrance.

**Keywords**: Persister cells, Bacteria, Relapse, Recalcitrance, Infection

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## Introduction

Bacterial persister cells are a subpopulation of bacteria that can be either produced stochastically during the logarithmic phase of bacterial growth (called type II persister) or induced by environmental stress such as lack of nutrients during the stationary phase of growth, antibiotic or oxidant stress, extreme pH, etc. (called type I persisters) (1,2). These dormant forms of bacteria, which are highly tolerant against harsh conditions, are counted as a savior mechanism in sake of the specific bacterial population from which they have raised and have been introduced into the scientific world mainly through in vitro experimental research (1-7).

## Historical Context and Research Progress

Although suspected for long (8), the first study that took direct experimental steps to link between the recalcitrance of chronic infections in patients and bacterial persister cells was provided by Mulcahy et al. in 2010 (9). After that, several other studies followed the same path in order to prove the causality between persister cells and relapsing infections (10-12), until now, which is generally accepted within the scientific society throughout the world that persister cells are one important cause of infection relapse (7, 13-15).

## Methodological Considerations in Persister Cell Research

Most of the mentioned studies have more or less followed a general procedure of collecting clinical samples suspected to contain bacterial persister subpopulation, culturing the samples to grow up and purify the bacterial agent, performing persister assay using either the antibiotic or the lysozyme protocols to kill the susceptible cells, followed by plating the remaining cells (known as persister cells) to quantify the number of persister cells in the main population (Figure 1). Nevertheless, by scrutinizing deeper into the literature, it seems that most of the above-mentioned investigations may share some misconceptions or imprecisions in the procedure of assessing persister cells from clinical samples, which might have led to some distortion of the conclusions. One such point is that culturing the clinical samples for ~24-72 hours before the persister assay will most likely resuscitate persister cells back to normal active cells, which disturbs the quantification procedure. It is inferred from several studies (1, 16) that persister cells start reverting back to normal cells within about 3 hours of incubation in nutrient media. The second point is that the persister assay using ~4-24 hours incubation time with antibiotics can itself induce the formation of persister cells and, therefore, a protocol like the lysozyme protocol (1) which requires an incubation time of less than 45 minutes seems to be more suitable for persister isolation from clinical samples. Another notion is the issue of viable but non-culturable (VBNC) state which needs to be differentiated from persister cells during all these procedures. VBNCs are also a drug-tolerant state of bacteria which, similar to persisters, but in higher numbers, are formed in both the logarithmic and stationary phases of bacterial growth (16, 17). Therefore, VBNCs could also be present, even in higher numbers, alongside persisters in the clinical samples and be responsible for the recalcitrance of infections. VBNC-persister differentiation has also been overlooked in many in vitro experiments working on different aspects and characteristics of persisters including genomics and proteomics. So, in general, in order to have a fair judgment on whether persisters are the culprit of relapse and recalcitrance of infections, a protocol should be undertaken which enables persister isolation directly from clinical samples rather than overnight cultures which provide the condition for persister resuscitation. In addition, the persister assay should be carried out in less than 45 minutes to avoid the induction of persisters by the protocol itself. Most importantly, the procedure should enable the distinction between VBNCs and persister cells in the clinical sample and should not induce the VBNC state either.

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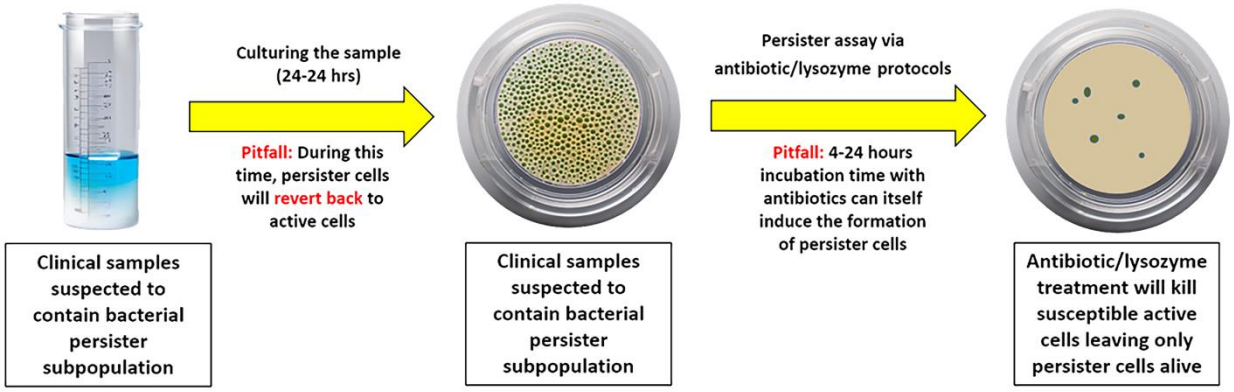



**Figure 1**. Schematic representation of the standardized process for quantifying bacterial persister subpopulations within clinical samples as described in relevant literature studies.

## Ambiguities in the "Persisters Cause Infection Relapse" Concept

Besides the above arguments, if we go over what actually happens during an infection, we find ambiguities and missing links which lead to doubt on what this article calls the “persisters cause infection relapse” idea. Further clarification of these un-answered queries are needed in order to certify the definite role of persister cells in the relapse of infections.

The infection process backing up the above mentioned idea, is as follows: 1) the otherwise healthy individual gets infected with bacteria, 2) the bacteria finds its suitable niche within the body by binding to complementing receptors and gets localized, 3) the bacteria starts to replicate and reach a detectable level for the immune system to start acting against the bacteria, 4) the patients manifests some signs and symptoms which might lead to antibiotic(s) prescription, 5) the immune system and the antibiotic(s), in addition to killing most of the bacterial cells, make the condition harsh for the bacteria, simultaneously inducing the formation of persister cells which tolerate the harsh condition, 6) due to the demise of most bacterial cells, the signs and symptoms of the patients subside within a few days of antibiotic therapy; however, since a small subpopulation of bacteria (known as persisters) are still alive, they start replicating as soon as the antibiotics are stopped and the immune response wanes off. This will lead to infection relapse.

The questions/ambiguities in some steps of the above infection process are as follows: 1) are the persister cells of the infecting bacteria formed during the logarithmic phase of growth inside the body or are they induced by the harsh condition caused by antibiotics and the host’s immune system? Since most, if not all, bacteria are able to form a fraction of ~ 10-6-10-4 persister cells (the exact fraction varies according to the bacterial strain) during the logarithmic phase of their growth as an innate bet-hedging mechanism (1, 9, 18-20), then this question will be raised as to why some infections, as opposed to others, will be easily cleared without any relapse. This is one notion against the idea of “persisters cause infection relapse”; because if persisters were responsible for the relapse, we would expect to see relapse in most, if not all, infections. 2) It is understandable why antibiotics are unable to kill the already formed persister subpopulation, since most antibiotics act on actively growing cells and persisters have entered into a non-growing dormant state.

However, why the immune system (including the innate and adaptive arms) which has well-equipped intelligent constituents to battle also against non-active cells, is unable to ward off these bacterial forms is a place of ambiguity. Antimicrobial peptides

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(AMPs) are peptides widely distributed in nature and are important elements of the innate immunity which impose their antimicrobial activity through different mechanisms either by acting on the surface or penetrating inside the foreign cells to interact with internal cellular components (21, 22). Most natural AMPs are membrane-acting peptides which do not need an actively growing cell to act upon (23) and, therefore, should be able to kill the invading bacteria as well as persister cells.

Furthermore, a literature review shows that most antimicrobial peptides for which anti-persister activities have been examined in vitro, are either synthetic, semi-synthetic, or extracted from non-human organisms (24-44). In order to understand whether or not naturally occurring AMPs in humans can really fend off against persister cells, it is necessary to assess the activity of a wide range of natural human AMPs against persister cells of a diversity of bacteria.

Besides AMPs, macrophages and dendritic cells are other important elements of the innate immunity which can phagocyte bacteria even if they have been forced into a static and non-growing form by different conditions including bacteriostatic antibiotics. Persisters, unless proved otherwise, do still have bacterial PAMPs (pathogen-associated molecular patterns) and foreign antigens on their surface which make them detectable to innate and adaptive immunity, respectively.

The persisters' evasion from the immune system cannot also be attributed to their low cell number or their ability to hide. If it is debated that the number of persister cells is below the detection level of the immune system, then several aspects should be considered for a comprehensive answer:

i. If the persister cells are formed during the logarithmic phase of the growth, then the number of cells would be low depending on the starting bacterial dose entered into the body (within a fraction of ~ 10-6-10-4 of the total population). If that is the case, it should be considered that the immune system is not confronted to a low dose of bacteria in the first place, but rather, the infecting bacterial dose will replicate, increase in its population size and produce a small fraction of persister cells alongside its replication. So, the immune system is not encountered with a small population below its detection level in the first place and should, therefore, be able to eradicate all the bacterial cells, with the help of PAMPs, surface antigens and appropriate receptors.

ii. If the persisters are induced by the antibiotics and the harsh conditions inside the body, then the fraction would increase to ~10-3-10-1 (16) and it would be unlikely for the immune system to be incapable of detecting this number of persister cells, not to forget that the condition of the starting bacterial dose (mentioned in the previous paragraph) would still apply in this case.

On the other hands, persisters' survival inside the body cannot be attributed to the ability of persisters to hide from the immune system, since actively growing cells could also skip to places out of reach of the immune system, and therefore, infection relapse by this mean could also happen by actively growing cells.

## Unanswered Queries and Areas for Further Research

Is it possible that the immune cells, including macrophages, dendritic cells, B or T cells, or other immune constituents, detect and act differently against persisters and active cells? Are persister cells formed inside the phagocytic immune cells? Is it possible that the membrane of persisters undergoes some modifications which make them unnoticeable to the immune guard? Do persister cells exist as a usual companion of the bacterial infections or are they really induced during the time of infection? If they are induced, where do they reside mostly during an infection? Which conditions within the body cause persister induction the most? (how much is it related to long antibiotic treatments?), How much would the relapse rate decrease among patients if appropriate

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anti-persister regimens are prescribed which de facto eradicate the persister cells? These questions, although arduous to answer, need elucidation through well-found research experiments which would assess the possible roles of persisters in relapsing infections as well as the action of different human immunity compartments against persister cells of a wide range of bacteria. Following the in vitro simulation of the human immune system to assess the above queries, further in vivo experiments on animal models need to complement the results, followed by final assessments in humans. Instances of found papers that have partly unveiled the contents of macrophages, in terms of bacterial states, after phagocytizing Salmonella Typhimurium and Mycobacterium tuberculosis, are those carried out by Helaine et al. in 2014 45) and Mouton et al. in 2016 (46), respectively. These studies have shown that internalization of Salmonella and Mycobacterium cells by macrophages, can itself provide the condition for persister induction. Helaine et al. have also shown that the persister induction for Salmonella Typhimurium is mostly due to vacuolar acidification and nutritional deprivation inside the macrophage. More studies like these are needed on different bacterial types and different immune components, to deliver us to an inclusive conclusion about what actually happens during different bacterial infections and whether or not/how persisters are playing roles in the relapse or recalcitrance of infections.

## Conclusion

In conclusion, unraveling the impact of bacterial persister cells on infection relapse demands precise methodologies and exploration of unanswered questions. Key considerations include methodological pitfalls, uncertainties about persister origins including the nuanced distinction between viable but non-culturable (VBNC) states and persister cells, immune responses, and the exploration of factors influencing persister cells. Hypothetical anti-persister regimens show promise, but a multidimensional approach, from in vitro to in vivo studies, is essential for comprehensive insights. Ongoing exploration, methodological refinement, and interdisciplinary collaboration are crucial for devising targeted strategies in infection control.

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## Conflict of interest

No conflict of interest declared.

## Authors' contributions

**PA** initiated the idea for writing the opinion article, prepared, and edited the first draft. **BSK** assisted in preparation and criticism of the first draft.

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