Commentary

# A Perspective on Microbubble Systems for Infectious Microenvironment Restoration and Antibiotic Delivery

**Maxwel Adriano Abegg**[1]

1. Graduate Program in Sciences, Technology and Health (PPGCTS), Federal University of Amazonas (UFAM), Brazil

**Multidrug-resistant (MDR) bacterial infections frequently occur in hostile microenvironments marked by acidic pH, hypoxia, oxidative stress, and biofilm formation—conditions that reduce antibiotic efficacy. While isolated attempts to restore individual microenvironmental factors, such as pH or oxygenation, have shown promise, they rarely address the full spectrum of physicochemical disruptions at infection sites. This work proposes a new strategy: the use of a programmed cocktail of microbubbles, with each population individually loaded with a distinct restorative agent (e.g., pH buffer, oxygen donor, redox modulator) and designed for ultrasound activation at the infection site. Optionally, these microbubbles may be targeted using antibodies to enhance site specificity. This modular approach enables the selective reprogramming of multiple aspects of the infectious microenvironment in situ, thereby improving the efficacy of subsequent or concomitant antibiotic action. In critically ill patients with MDR infections, even modest improvements in local drug performance may be decisive for clinical outcomes. By integrating developments in microbubble engineering, ultrasound-triggered release, and microenvironment modulation, this article outlines a potential path forward in adjunctive therapy for challenging bacterial infections.**

**Correspondence:** papers@team.qeios.com — Qeios will forward to the authors

Multidrug-resistant infections remain one of the most urgent global health challenges. Although antibiotic development has long focused on enhancing potency, there is increasing recognition that the local pathophysiology of infection sites—typically marked by acidosis, hypoxia, oxidative stress, and biofilm formation—plays a decisive role in therapeutic failure[1][2][3]. These environmental barriers can

impair drug uptake, destabilize antibiotics, suppress immune function, and create physical barriers that complicate treatment—particularly in chronic and recalcitrant infections.

Evidence from cancer research highlights the potential of local microenvironment modulation. In oncology, ultrasound-targeted microbubble destruction has been shown to remodel tissue architecture, normalize pH, improve perfusion, enhance oxygenation, and increase drug penetration—collectively boosting therapeutic outcomes[4]. Comparable pathophysiological features exist in infected tissues. Microbubbles are especially attractive for this context due to their biocompatibility, high loading capacity for oxygen and drugs, and ultrasound-triggered release capabilities[5]. These features enable precise, localized delivery with minimal systemic exposure.

Recent studies underscore the value of ultrasound-activated carriers for delivering oxygen, pH modulators, and antibiotics to resistant infection sites[6][7]. Stimuli-responsive systems—including nanocarriers and microbubble–nanoparticle hybrids—offer targeted, on-demand delivery that improves drug access to biofilms and enhances efficacy in challenging microenvironments[8][9][10].

Another critical development is the use of "sonobactericide"—ultrasound-activated microbubbles that disrupt biofilms and increase antibiotic penetration—dramatically improving infection control[11]. These platforms can be designed to respond to endogenous stimuli (e.g., pH, bacterial enzymes) or external triggers (e.g., ultrasound), ensuring highly tailored drug delivery. Multifunctional coatings and biomimetic designs further improve selectivity and biocompatibility[10].

This progress supports a conceptual shift: rather than intensifying antibiotic action alone, restoring physiological conditions at the infection site may improve the performance of existing drugs. Preclinical studies have shown that buffering pH, providing oxygen, and dispersing biofilms all enhance antibiotic efficacy in infected tissues[12][13][14].

Building on these findings, this article proposes a strategy centered on antibody-targeted microbubble systems to deliver restorative agents locally. Microbubbles—already FDA-approved as contrast agents—are compatible with a wide range of encapsulated contents and can release them in response to ultrasound. Their use in imaging makes them ideal theranostic agents for clinical translation[15][14].

A key advantage is the ability to focus ultrasound at the infection site, triggering release in a spatially controlled, real-time manner. This approach reduces systemic exposure and allows smaller, more targeted doses to be therapeutically effective.

A critical consideration is determining appropriate doses for each agent. Given the variability of infection microenvironments, optimal amounts of oxygen donors, redox modulators, or pH buffers will differ across clinical contexts. Dose selection must be guided by empirical studies and may follow the model of iterative optimization seen in oncology combinations[12][13].

Microbubble systems are best suited to antibiotics with intravenous formulations, consistent with current practices in severe MDR infections[3]. Although microbubbles have a lower loading capacity than some nanocarriers, repeated injections and targeted delivery can generate sufficient local concentrations[16][15].

Instead of encapsulating multiple agents in one microbubble, we propose a modular approach: administering a cocktail of microbubbles, each loaded with a single restorative agent (e.g., sodium bicarbonate for buffering, perfluorocarbons for oxygenation, catalase mimetics for redox modulation). This reduces incompatibility risks and allows tailored therapy based on patient-specific needs.

The antibiotic may be delivered as a separate microbubble population or as a standard IV infusion timed to follow the restorative cocktail. Although local drug concentrations are lower than in systemic regimens, even modest targeted doses have proven effective in preclinical settings[13][14]. Further studies are needed to refine dosing and assess clinical benefit.

This cocktail-based model also supports personalized therapy. Both the microbubble contents and the timing of antibiotic administration can be tailored to infection characteristics—e.g., oxygen donors for hypoxia, redox modulators for high oxidative stress. This enables flexible, environment-guided interventions.

The most practical clinical workflow might involve administering the microbubble cocktail to recondition the infection site, followed by an immediate IV antibiotic infusion to capitalize on this therapeutic window. This approach may enhance antibiotic performance and offer a translational path forward.

Compatibility between agents has been established in prior studies using microbubbles and related carriers[16][17][18]. Encapsulating one agent per bubble and adding stabilizers minimizes interactions, while drug stability is preserved until release[15][12].

This strategy should be seen as adjunctive, not curative: a temporary restoration of the microenvironment that favors antibiotics and immune cells. Its justification lies in evidence linking acidosis, hypoxia, and oxidative imbalance to treatment failure[1][2].

Importantly, the use of ultrasound and microbubbles benefits from an existing safety record. Though regulatory and cost hurdles remain, many components are already used in critical care. The novelty lies in their combined use and targeted delivery.

Additionally, this strategy could unlock the clinical use of antibiotics that are normally avoided due to high systemic toxicity (e.g., colistin, aminoglycosides). Delivered in a localized, low-dose form via ultrasound-activated microbubbles, such agents may provide a new therapeutic option for critically ill patients with few alternatives. Similarly, drugs typically restricted to oral or topical use could be repurposed: when encapsulated in microbubbles and delivered intravenously, even minimal local concentrations may work synergistically with standard treatments to control otherwise refractory infections. By combining microenvironment modulation with spatially controlled drug delivery, this approach could provide life-saving flexibility in desperate clinical scenarios.

Although antibody-mediated targeting might enhance specificity, it adds complexity and cost. A more practical approach may be untargeted IV delivery followed by focused ultrasound activation at the infection site. This leverages the natural accumulation of microbubbles in inflamed tissues and ensures site-specific release[4][11]. Antibody functionalization is therefore optional and may be reserved for special cases.

In summary, targeted microbubble-based restoration of the infectious microenvironment offers a promising adjunctive strategy for enhancing antibiotic efficacy in MDR infections. This proposal is well grounded in preclinical evidence, and future studies should assess its translational potential in human infections.

## Statements and Declarations

### *Conflict of Interest*

The author declares no conflict of interest.

### *Authors' Note*

Artificial intelligence tools (ChatGPT-4o, GPT-4.1-mini) were used to support the integration of cross-disciplinary references, comparative evaluations, and feasibility insights, but all scientific ideas, content, interpretation, and synthesis are the author's own.

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## Declarations

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