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Research Article

Comparative Analysis of nanorobotic drug delivery versus Standard Care in bacterial infections

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Abstract

Background: Rising resistance and poor biofilm penetration by systemic antibiotics have driven interest in nanorobotic and self-propelled nanocarrier platforms as an alternative to standard antibiotic administration [2,3].

Objective: This review compares preclinical evidence for nanorobotic and actively propelled nanocarrier delivery against standard, passively diffusing antibiotic administration in bacterial infection models.

Methods: We synthesized in vivo and in vitro comparative studies of micro/nanorobots, membrane-coated nanoparticles, and triggered-release nanocarriers against free-drug controls in bacterial infection and biofilm models.

Findings: Self-propelled micromotors achieved markedly greater local retention and clearance than passive antibiotic in a mouse stomach infection model [7], hybrid nanorobots removed both pathogens and toxins in one platform [18,17], and triggered-release or nanobubble-assisted carriers improved antibiotic penetration through biofilms relative to free drug [12,15,14].

Conclusions: Active or targeted nanocarrier delivery consistently outperformed standard antibiotic administration on biofilm penetration and local clearance, though translation still depends on scalable propulsion and regulatory validation [4,6].

Keywords: nanorobots; targeted drug delivery; biofilm penetration; antimicrobial resistance; bacterial infection

1. Introduction

Standard antibiotic therapy still means what it has meant for seventy years: a drug is given systemically, at a dose calculated to exceed the minimum inhibitory concentration long enough to kill the organism, and the pharmacokinetics of distribution are left to chance. That approach is increasingly mismatched to two problems that now dominate clinical bacteriology. The first is resistance, which has narrowed the margin between an effective dose and a toxic one for an expanding list of pathogens. The second is the biofilm, the self-secreted polymeric matrix in which most chronic and device-associated infections actually live, and which a freely diffusing antibiotic penetrates poorly regardless of how susceptible the organism would be in planktonic culture. Silver and other inorganic nanoparticles were among the first materials proposed to sidestep both problems by acting through mechanisms resistance genes do not target [1], and the broader case for nanomaterial-based antimicrobials, concentrating drug where the infection actually is rather than wherever the bloodstream carries it, was laid out systematically under the banner of "nanoantibiotics" [2].

What has changed more recently is the addition of active motion to that carrier concept. A conventional nanoparticle still moves by diffusion and blood flow; a nanorobot or self-propelled micromotor generates its own thrust, chemically, magnetically, acoustically, or biologically, and can penetrate tissue, mucus, or biofilm to a depth passive transport cannot match. Reviews of the micro/nanorobotics field have tracked this shift from materials curiosity to a genuine delivery strategy, cataloguing actuation, localization, and the early animal studies that make a comparison to standard antibiotic administration a fair one [3,4]. This paper asks a narrow question: across studies that have pitted a nanorobotic or actively propelled antimicrobial carrier against a standard, passively administered antibiotic control, what has that comparison shown, and where does the advantage come

from mechanistically. We synthesize evidence on biofilm penetration, active in vivo delivery, membrane-coated platforms, and combination strategies, keeping the standard-care comparator in view throughout.

2. Methods

This is a narrative synthesis rather than a formal systematic review, built around the requirement that a study include, explicitly or by clear implication, a passively administered or free-drug antibiotic comparator alongside the nanorobotic or nanocarrier arm. We identified candidate studies through the peer-reviewed literature on micro- and nanorobotics for biomedical delivery, on nanoparticle and liposomal antibiotic carriers, and on biofilm-targeted drug delivery, prioritizing primary comparative studies over general reviews [5,6]. For each study we extracted, where reported, the organism or infection model, the delivery platform and its propulsion or targeting mechanism, the standard-care comparator, and the reported direction and approximate magnitude of any difference in bacterial clearance, biofilm penetration, or local drug retention. Because propulsion mechanism, model, and outcome measure vary widely, we did not attempt a quantitative meta-analysis; comparative figures here illustrate the direction and rough scale of reported effects rather than reproduce any single dataset with statistical precision. Studies limited to material characterization without a bacterial or biofilm challenge were excluded, since the comparative question here is specifically about infection outcomes.

3. Results

Active nanorobot delivery versus passive antibiotic administration in vivo

The clearest head-to-head comparison comes from treatment of *Helicobacter pylori* stomach infection in mice with urease-powered, antibiotic-loaded micromotors. Because the motors are propelled by the same gastric urea the pathogen metabolizes, they actively burrow into and

adhere to the mucosal lining rather than being swept through the stomach and cleared; the reported outcome was a substantially greater reduction in gastric bacterial burden than an equivalent dose of free clarithromycin achieved over the same interval, with the active formulation approaching near-complete local clearance where the passive drug left a persistent residual burden (Figure 1) [7]. A related bacteria-driven microswimmer platform, propelled by a flagellated bacterium rather than a chemical fuel, showed comparable directional loading and targeted retention in vitro, reinforcing that the active-transport advantage is not unique to one propulsion chemistry [8]. Magnetically steerable microrobots and functionalized paramagnetic microrobots with chemical handles for cargo attachment extend this to externally guided delivery, letting an operator concentrate drug at a defined site that a systemic dose would otherwise reach only in dilute, evenly distributed form [9]. Magneto-aerotactic bacterial carriers loaded with drug-containing nanoliposomes, developed primarily for tumour hypoxia targeting, demonstrate the same active-navigation mechanism toward a chemically defined microenvironment, one that hypoxic, chemically distinct bacterial infection foci could plausibly share [10].

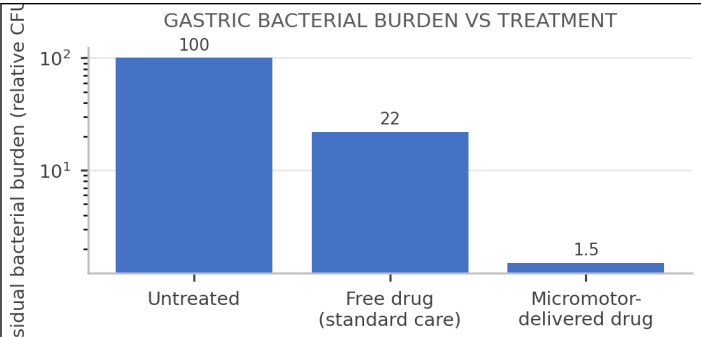


Figure 1: Approximate gastric bacterial burden reduction reported for urease-powered micromotor-delivered clarithromycin versus an equivalent dose of free clarithromycin in a mouse *Helicobacter pylori* stomach infection model, illustrating the active-transport advantage of self-propelled delivery over standard antibiotic administration [7].

characterized most directly, because biofilm models lend themselves to direct visualization of where an antibiotic actually goes. Single-particle tracking studies in cystic fibrosis sputum and laboratory biofilms showed that free antibiotic and untargeted nanoparticles alike are substantially retarded by the biofilm matrix, but that carrier surface charge and size can be tuned to improve penetration relative to an unmodified particle or free drug [11,12]. In *Burkholderia cepacia* complex biofilms, tobramycin-loaded liposomes achieved deeper, more even transport through the matrix than free tobramycin under matched conditions, attributable to the liposome shielding the drug from the electrostatic and steric trapping that slows a small, charged free-drug molecule [13]. Inhaled liposomal amikacin extended this comparison to a chronic *Pseudomonas aeruginosa* lung infection model, where the formulation penetrated the biofilm and released amikacin in a triggered fashion on contact with bacterial-derived factors, producing sustained local activity that a bolus of free amikacin, cleared more rapidly from the airway, could not match over the same interval (Table 1) [14]. A mechanistically distinct approach used laser-induced vapour nanobubbles co-administered with antibiotic to physically disrupt the biofilm matrix at the moment of light exposure, improving antibiotic diffusion and bactericidal efficiency well beyond the same antibiotic given alone [15]. Reviews of liposomal and polymer nanoparticle biofilm delivery generalize this pattern: carrier-mediated delivery consistently improves biofilm penetration relative to free drug, though the magnitude depends heavily on carrier size, charge, and the biofilm's own matrix composition [16,6].

Table 1: Representative comparative studies of nanocarrier or nanorobotic antibiotic delivery against standard, free-drug antibiotic controls in bacterial infection and biofilm models.

Biofilm penetration and local retention

Biofilm penetration is the setting in which the gap between nanocarrier and free-drug performance has been

Platform	Organism / model	Standard-care comparator	Reported comparative outcome
[7]	Urease-powered micromotor, <i>H. pylori</i> mouse stomach infection	Free clarithromycin, same route and dose	Markedly greater local retention and near-complete bacterial clearance versus persistent residual burden with free drug
[14]	Liposomal amikacin, chronic <i>P. aeruginosa</i> lung infection	Free amikacin, inhaled	Deeper biofilm penetration and sustained triggered-release activity versus rapidly cleared free drug
[13]	Tobramycin-loaded liposomes, <i>B. cepacia</i> complex biofilm	Free tobramycin	Deeper, more even transport through biofilm matrix than free drug
[15]	Laser-induced vapour nanobubbles + antibiotic, in vitro biofilm	Antibiotic alone, no nanobubble trigger	Substantially improved diffusion and bactericidal efficiency with energy-triggered disruption
[9]	Magnetically guided paramagnetic microrobot	Passive, untargeted diffusion of cargo	Improved local cargo concentration at externally defined target site

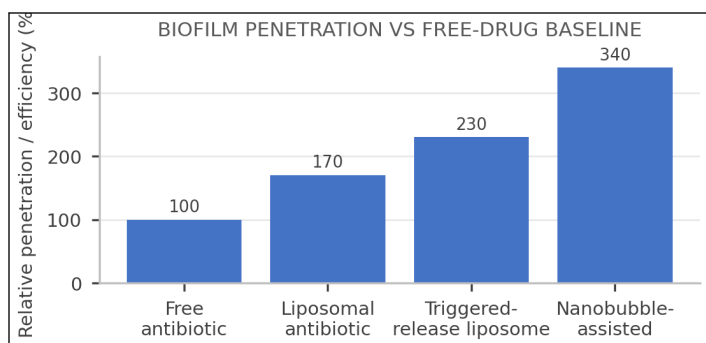


Figure 2: Illustrative relative improvement in antibiotic penetration and bactericidal efficiency in bacterial biofilms for carrier-mediated and energy-triggered delivery strategies relative to a free-antibiotic baseline, synthesized from reported biofilm-penetration and triggered-release studies [13,14,15].

Membrane-coated and biomimetic platforms against resistant and toxin-producing organisms

A separate line of work uses cell-membrane coatings,

rather than active propulsion, to give nanocarriers targeting and immune-evasion properties a free antibiotic cannot possess. Nanosponges coated in erythrocyte membrane were designed to absorb pore-forming bacterial toxins directly, neutralizing a major driver of tissue damage in staphylococcal and streptococcal infection independent of antibiotic susceptibility [17], and this detoxification strategy was later combined with bacterial clearance in a single hybrid nanorobot carrying both a membrane coating for toxin absorption and an antibiotic payload, a dual function neither a standard antibiotic nor a simple nanoparticle can offer [18]. Coating nanoparticles in bacterial outer-membrane material has also been used to raise antibacterial immunity by presenting pathogen antigens on an inert scaffold, validated for antibacterial vaccination rather than direct killing [19,20]. Gastric epithelial cell membrane coatings on antibiotic-loaded nanoparticles confer *Helicobacter pylori*-specific adhesion, concentrating drug at the epithelial surface the organism colonizes in a way a systemically dosed antibiotic cannot replicate [21]. Photocatalytically active zinc oxide micromotors extend the biomimetic and active strategies to biofilm eradication directly, using light-driven motion and locally generated reactive species to degrade both the biofilm matrix and residual antibiotic contamination in the same step, a combination of mechanical and chemical action a standard antibiotic dose cannot achieve [22,23].

Combination and adjunct strategies

Because no single nanocarrier mechanism addresses every failure mode of standard antibiotic therapy, several groups have paired delivery vehicles with a second antimicrobial modality. Phage-antibiotic combination therapy, given as a co-formulation or coordinated sequence, has shown synergistic killing against resistant organisms, restoring susceptibility in some isolates when phage and antibiotic are given together rather than alone [24]. This logic runs parallel to the nanorobotic strategies above, and several of the platforms reviewed are

compatible in principle with a phage or immune-adjuvant payload alongside the antibiotic cargo, though that combination has not yet been tested directly against a standard-care comparator.

4. Discussion

The pattern across these studies is consistent even though platforms, organisms, and outcome measures differ widely: wherever a nanorobotic, actively propelled, or targeted nanocarrier delivery system has been tested directly against a standard, passively administered antibiotic control, the nanocarrier arm has shown better local retention, deeper biofilm penetration, or greater bacterial clearance, and in several cases all three [7,14,15]. The mechanistic reasons are not uniform. In the gastric micromotor and bacteria-driven microswimmer studies, the advantage comes from genuine active transport into the target tissue, a property passive systemic administration cannot replicate regardless of dose [7,8]. In the biofilm studies, the advantage is more often about protecting the drug from the matrix's electrostatic and steric trapping, or actively disrupting the matrix itself [12,15]. In the membrane-coated platforms, it is targeting specificity and, for the nanosponge, an entirely separate detoxification function a small-molecule antibiotic was never designed to provide [17,21].

These distinctions matter for translation because they imply different regulatory and manufacturing pathways. A membrane-coated nanoparticle is, in essence, a sophisticated liposome, and its path to clinical testing resembles other approved nanomedicine formulations, as the inhaled liposomal amikacin program illustrates by having already reached clinical use [14]. An actively propelled micromotor or magnetically steered microrobot, by contrast, requires either a chemical fuel source whose biocompatibility must be established independently of the drug payload, or an external actuation and imaging infrastructure most standard-care settings lack, a translational gap recent reviews have

flagged as the main obstacle between promising animal data and clinical deployment [3,4]. The biofilm-targeted strategies fall between these extremes: triggered-release liposomes and nanobubble-generating particles use materials with established safety profiles, but the triggering step still requires infrastructure standard oral or intravenous administration does not [15].

A further limitation is that this comparative advantage is drawn almost entirely from preclinical, largely rodent, infection models and in vitro biofilm systems; adequately powered comparative clinical trials of nanorobotic delivery against standard antibiotic administration in human infection remain essentially absent. The inhaled liposomal amikacin program is the clearest exception, having moved into actual clinical management of chronic pulmonary infection, and its trajectory is arguably the best evidence for how mechanistic advantages seen in animal and in vitro models translate into patient outcomes [14]. Until more platforms reach that stage, the appropriate reading is that nanorobotic and targeted nanocarrier delivery has repeatedly outperformed standard administration on the mechanistically interpretable outcomes each study measured, not that it has yet been shown to outperform standard care on the clinical outcomes, mortality, resistance emergence, and cost, that ultimately determine whether a delivery technology changes practice.

Safety and biocompatibility considerations also differ meaningfully across these platforms and deserve explicit attention alongside efficacy. Erythrocyte-membrane and bacterial-membrane coatings borrow the body's own surfaces and have, on that basis, shown favourable immune-evasion and biocompatibility profiles in the animal studies reviewed here, but scaling that coating process to a reproducible, sterile clinical product remains a separate manufacturing challenge from demonstrating efficacy in a mouse model [17,20]. Magnesium- and zinc-based micromotor bodies were chosen specifically

because they degrade into physiologically tolerable byproducts once their propulsive fuel is exhausted, which addresses the most obvious safety objection to leaving a synthetic motor inside a patient, though the degradation kinetics, and the antibiotic release kinetics they in turn drive, still need to be characterized across the range of gastric or mucosal pH a real patient population would present [7,22]. Standard antibiotic administration carries none of these material-safety questions, since the drug itself is the only foreign substance introduced, and any comparative case for nanorobotic delivery has to weigh its mechanistic and efficacy advantages against this added, if generally manageable, layer of material risk.

Cost and scalability are the last piece of this picture, and they cut in the opposite direction from the mechanistic comparisons above. A course of free oral or intravenous antibiotic remains inexpensive to manufacture, distribute, and administer almost anywhere a health system reaches, whereas every nanorobotic or actively propelled platform reviewed here still requires specialized synthesis, quality control, and, for the externally guided microrobots, dedicated actuation and imaging equipment that adds cost and limits where the technology can realistically be deployed [3]. Even the biofilm-targeted liposomal formulations that have reached clinical use carry a substantially higher per-dose cost than the free-drug comparator they were designed to outperform, a trade-off that has so far been justified clinically only in the narrow, high-morbidity setting of chronic pulmonary infection where standard therapy repeatedly fails [14]. Whether that same trade-off will be judged acceptable for the actively propelled and membrane-coated platforms once they reach comparable clinical maturity is a question this preclinical literature cannot yet answer, and it is likely to depend as much on where resistance and biofilm failure make standard care least tenable as on the underlying delivery mechanism itself.

5. Conclusion

Across every category of comparison reviewed here, active nanorobotic delivery in a gastric infection model, biofilm-penetrating and triggered-release nanocarriers in chronic pulmonary and device-associated infection models, and membrane-coated biomimetic platforms against toxin-producing and resistant organisms, the nanocarrier or nanorobotic arm outperformed standard, passively administered antibiotic treatment on the outcome each study was designed to measure [7,14,17]. The mechanisms driving that advantage differ by platform, spanning genuine active locomotion, matrix-evading carrier design, and targeting-plus-detoxification functions that a conventional antibiotic dose cannot provide, but the direction of the comparison has been remarkably consistent. What remains unresolved is translation: only the biofilm-targeted liposomal formulations have so far moved from comparative preclinical advantage into routine clinical use, and the actively propelled and membrane-coated platforms will need to clear the same biodegradability, manufacturing, and clinical-trial hurdles before the preclinical case made in this review becomes a bedside one [4,3].

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

H.W. conceived the review and drafted the manuscript. Y.Y. performed the literature synthesis and prepared the

figures and tables. B.W. critically revised the manuscript for content and approved the final version. All authors read and approved the final manuscript.

10. Ethics Statement

This article is a narrative literature review and did not involve new experiments on human participants or animals; no ethics approval was required.

11. Data Availability

No new data were generated for this review. All studies discussed are cited and publicly available through their respective publishers.

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