RESEARCH PAPER

Efficacy and safety of phage therapy in the management resistant bacterial infections: Systematic review

Lilian Medina [1], Ana Pomagualli [1], Johanna Champang [2], Elizabeth Conterón [2], Ana Guerra [3], José Herrera [4]

[1]Maestrante de postgrado, Facultad de Ciencias de la Salud, Universidad Técnica de Ambato-Ecuador; orcid.org/0009-0008-9035-4596 (L.M.); orcid.org/0009-0003-5135-9283 (A.P.)
[2]Laboratorista clínico, Hospital General Francisco de Orellana-Ecuador; orcid.org/0009-0001-3348-4326 (J.Ch.); orcid.org/0009-0000-8770-0058 (E.C.)
[3]Laboratorista clínico, Centro de salud tipo "B" Pallatanga-Ecuador; orcid.org/0009-0000-3161-6762 (A.G.)
[4]Docente, Facultad de Ciencias de la Salud, Universidad Técnica de Ambato-Ecuador; orcid.org/0000-0002-6061-0156 (J.H)

Abstract
Phage therapy is a therapeutic treatment that involves the use of bacteriophages, with significant potential for the treatment of antibiotic-resistant bacterial infections. This method provides a specific and natural alternative that targets only pathogens without harming the beneficial host microbiota. Objective: To synthetize the available evidence regarding the efficacy and safety of phage therapy compared with antibiotic treatment for infections caused by resistant bacteria. Methodology: A systematic review was conducted based on articles published in major academic databases, including Scopus, PubMed, Springer, and Google Scholar, using Boolean operators and filters specific to each database. A total of 185 articles were identified, of which 19 met the inclusion and exclusion criteria established for this review. Results: The evaluated randomized trials, case reports, and meta-analyses indicated that phage therapy (topical and intravenous) achieved microbial reduction rates and clinical resolution in a high percentage of patients considered to have conventional therapeutic options. The safety profile was favorable, with very few adverse events, most of which were mild, transient reactions associated with the release of bacterial endotoxins. Conclusion: The findings of this review suggest that phage therapy is an effective intervention for the management of severe infections caused by resistant bacteria, indicating its potential as a complement or alternative to antibiotic treatments. However, there is a clear need for longitudinal studies to consolidate its integration into formal medical practice.

Keywords: Phage therapy; Bacteriophages; Bacterial Infections; Treatment Outcome

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1. Introduction

Phage therapy is a therapeutic strategy that involves the use of bacteriophages [or phages] to infect and lyse specific pathogenic bacterial strains, representing a promising alternative to traditional antibiotics [1]. From a microbiological perspective, phages are ubiquitous biological entities with high specificity toward certain bacterial hosts, thus reducing concomitant damage to beneficial microbiota [2]. In the clinical setting, its use is relevant in the context of multidrug-resistant (MDR) bacterial infections, where antibiotic options are limited or non-existent [3].

From a molecular perspective, the mechanism of action involves the phage adhering to specific receptors on the bacterial surface, injecting its genetic material, and subsequently undergoing lytic replication, which results in destruction of the host cell and the production of new phages [4]. Despite its potential, the implementation of phage therapy faces regulatory and logistical challenges, such as the standardization of preparations and the need for robust clinical trials to support its efficacy and safety in humans [5]. However, the resurgence of interest in this mode of therapy reflects a necessary strategy within the "One Health" paradigm to address the global crisis of antimicrobial resistance [6].

The origins of phage therapy date back to its discovery by the microbiologists Frederick Twort and Félix d'Herelle in 1915, who introduced the term "bacteriophage" and proposed it as a treatment for bacillary dysentery [7]. Throughout the 1920s and 1930s, its use spread worldwide for the treatment of bacterial infections such as cholera and Staphylococcus aureus infections [8]. However, the advent of the "golden age of antibiotics" in the 1940s relegated their use mainly to the Soviet Union and Eastern Europe, where they continued to be used empirically [9].

The resurgence of global interest began at the end of the 20th century and has accelerated in the 21st century, driven by the growing crisis of antimicrobial resistance. The scarcity of new classes of antibiotics has positioned phage therapy as a viable alternative, leading to an increase in the number of studies and published clinical cases seeking to establish its efficacy [10,11].

*Author for Correspondence: Lilian Medina

In this regard, the World Health Organization (WHO) has classified antimicrobial resistance as one of the ten major threats to global public health and, consequently, highlighted the urgency of researching alternatives such as phage therapy. According to the most recent estimates, infections caused by resistant bacteria were responsible for approximately 1,27 million attributable deaths worldwide in 2019, with this figure expected to rise to 10 million annually by 2050 [12] if effective measures are not implemented. This critical scenario emphasizes the urgent need to develop and validate new effective therapeutic strategies, positioning phage therapy as a candidate of great importance within the therapeutic arsenal in the face of this silent crisis.

Many researchers worldwide have investigated this topic. For example, in Russia, Fedorov et al. conducted a prospective, non-randomized study involving 45 patients with prosthetic hip joint infection to evaluate the efficacy of combined phage and antibiotic therapy compared with antibiotic-only treatment after surgery. The results indicated that the relapse rate was much lower in the group that received combination therapy [4,5 % vs. 36.4 %], with a treatment effectiveness of 95,5 % compared with 63.6% in the control group, demonstrating that the combination of phages and antibiotics is almost 12 times more effective in preventing hip relapses [13].

Systematic reviews, such as the one conducted in Italy by Cocorullo et al., have also concluded that phage therapy represents a promising alternative for the treatment of multidrug-resistant bacterial infections in patients with cystic fibrosis (CF), demonstrating efficacy in compassionate use situations against pathogens such as Pseudomonas aeruginosa, Mycobacterium abscessus, and Burkholderia spp. [14].

Similarly, in another systematic review conducted by Al-Anany et al. in Canada including 55 studies on phage therapy for urinary tract infections, more than 72% of the articles reported both microbiological and clinical improvements, demonstrating that phage therapy is a potentially safe and effective option for the treatment of UTIs, even those caused by antibiotic-resistant bacteria [15]. However, of the 55 documents analyzed, only 5 were randomized controlled trials, highlighting the need for larger and better-structured clinical trials to determine its long-term efficacy and safety.

In Latin America, the subject has also been investigated through systematic reviews. In Colombia, Aragana analyzed 27 studies involving 165 patients, revealing that phage treatment was 81% effective in reducing or eliminating bacterial load, while combined phage and antibiotic therapy achieved 100 % success [16].

This review was conducted due to the growing crisis of antimicrobial resistance and the urgent need to investigate therapeutic alternatives such as phage therapy. Compiling the latest evidence from clinical trials, case reports, and meta-analyses, this study aims to provide a comprehensive and up-to-date analysis regarding the efficacy, safety, and applicability of bacteriophages in the treatment of multidrug-resistant infections.

The main benefit of this critical review is providing the scientific community with a consolidated knowledge base demonstrating the potential of phage therapy either as monotherapy or in combination with antibiotics to achieve successful clinical outcomes in cases with complex infections, while identifying current gaps in knowledge and highlighting the need for standardization and larger studies to facilitate its integration into conventional clinical practice.

Therefore, the objective of this review is to synthesize the available evidence on the efficacy and safety of phage therapy compared with antibiotic treatment for infections caused by resistant bacteria. Therefore, the PICO question for this review is as follows: How efficient and safe is phage therapy, compared with conventional antibiotics, for the treatment of patients with antibiotic-resistant bacterial infections? In this case, P denotes patients with antibiotic-resistant bacterial infections, I denotes phage therapy, C denotes antibiotic treatment, and O denotes efficacy and safety.

2. Materials and Methods

This research was based on a systematic review of the literature in databases such as Scopus, PubMed, Google Scholar, and Springer, using the keywords “Phage therapy”, “Bacteriophages”, “Bacterial infections”, and “Treatment Outcome”. The search was adjusted, according to the established inclusion and exclusion criteria, based on the Boolean descriptors and filters used by each database.

The identification and selection of studies was carried out between November 2025 and January 2026 by four authors, each using a different academic database, while any doubts or discrepancies were resolved through discussion with the entire team of authors.

Inclusion criteria: Primary articles, full texts, clinical cases, randomized trials, and meta-analyses published in any language between 2021 and 2025 were included.

Exclusion criteria: Preclinical studies, animal studies, and duplicate studies were excluded from the review.

The guidelines established in the PRISMA (Preferred Reporting Items for Systematic Reviews and Mata-Analyses) statement were followed for the selection of articles. The PRISMA flow chart illustrates the identification of articles. The PRISMA flow chart shown in Figure 1 illustrates the identification, selection, and inclusion of articles. In addition, the selected documents were imported into Mendeley—a bibliographic reference management software—to check for duplicate studies between databases.

Procedure

The articles were initially evaluated by reading their titles and abstracts. All those that did not meet the inclusion criteria were discarded. Subsequently, the full texts were analyzed to discard further articles that did not meet the inclusion criteria, thus obtaining the final articles included in this review.

The literature search yielded a total of 180 articles, distributed as follows: 22 in PubMed obtained using the following search string ((("Phage Therapy"[Mesh]] OR

" Bacteriophages"[Mesh]) AND " Bacterial Infections "[Mesh]) AND "Treatment Outcome"[Mesh]); 55 in Springer using the search string (Bacteriophages OR Phage Therapy AND multidrug-resistant bacteria); 94 in Google Scholar using the search string ("Efficacy" +'safety' +"phage therapy"+"management of bacterial infections"); and 9 in Scopus using the search string (Bacteriophages OR Phage Therapy AND multidrug-resistant bacteria NOT mice).

Ten duplicate articles were excluded, reducing the number of documents to 170. Subsequently, 107 articles were excluded after reading the titles, 35 after reading the abstracts, and 8 after reading the full texts, reducing the number to 20 articles. In addition, two studies that met the review criteria were identified in the references of the selected studies are subsequently included. In total, 22 studies were included in the final analysis.

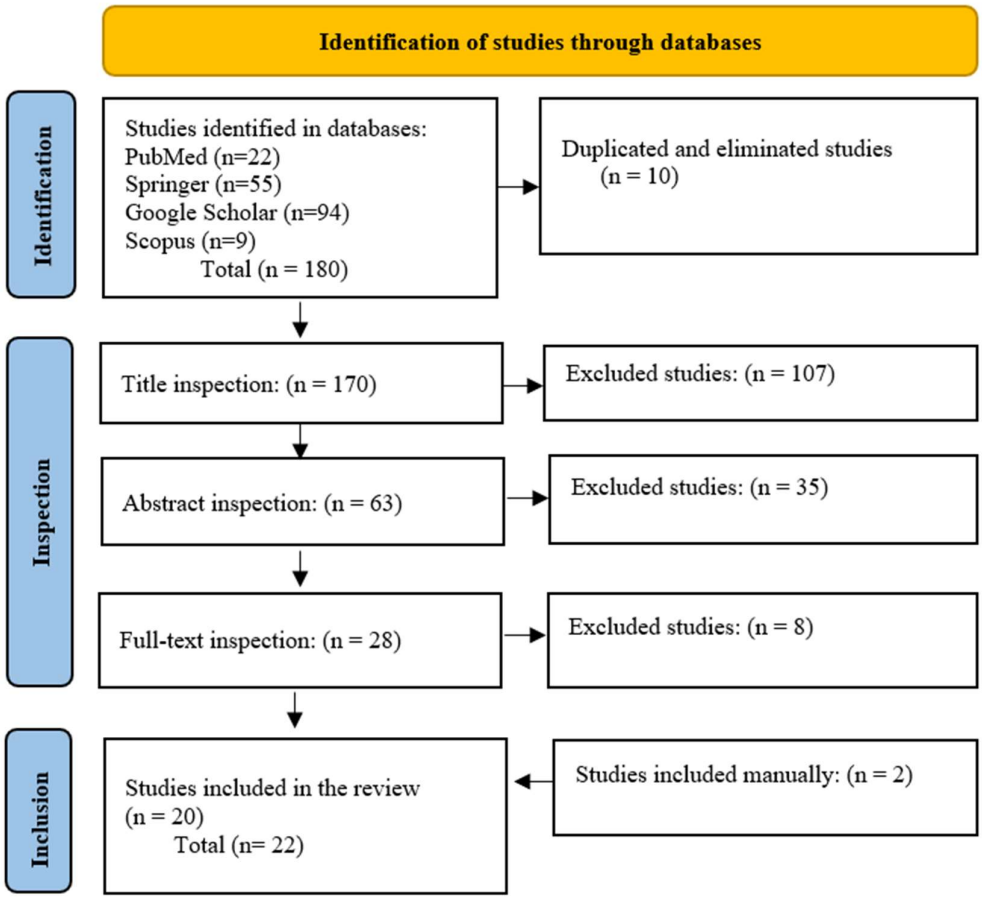

Figure 1. ***Identification, selection, and inclusion of studies.***

3. Results

Table 1 presents a summary of the methodological characteristics and most relevant findings of updated randomized clinical trials analyzing the efficacy and safety of phage therapy for the treatment of resistant bacterial infections. These studies indicate that topical, intravesical, or nebulized administration of bacteriophage cocktails either as monotherapy or in combination with antibiotics shows remarkable effectiveness in reducing bacterial load, healing chronic wounds, and improving clinical outcomes in patients with complex infections such as diabetic foot ulcers, cystic fibrosis, chronic rhinosinusitis, and urinary tract infections. In addition, favorable safety profiles and the ability of phages to act synergistically with antibiotics are noteworthy, reinforcing their potential as a therapeutic alternative in the context of antimicrobial resistance.

Table 1. *Characteristics of randomized trials.*

Author (year)	Design / Sample	Infection / Intervention	Key Outcomes
Karn et al. (2024), India [17]	RCT, double-blind, n=60	Chronic wounds; topical phage cocktail vs placebo + standard care	93.3% sterilization at 39 days; complete healing at 90 days; placebo: 83.3% persistent colonization

Nir-Paz et al. (2025), Israel [18]	RCT, n=19	Diabetic foot ulcers; topical TP-102	80% bacterial reduction vs 50% placebo; well tolerated
Dobretsov et al. (2021), Russia [19]	RCT, n=40	Chronic rhinosinusitis; phage gel (Otofag)	Significant reduction in total microbial load and Enterobacteriaceae
Kofi (2024), USA [20]	RCT, n=128	CF, MDR *P. aeruginosa*; phage + antibiotics	67.2% bacterial reduction vs 28.1% control; 78% biofilm reduction; improved lung function
Krakhotkin (2025), Russia [21]	Prospective comparative, n=178	Recurrent cystitis; phages ± antibiotics	Combination therapy superior for symptom relief
Leitner et al. (2021), Switzerland [22]	RCT, n=81	UTI; intravesical phage vs placebo vs antibiotic	Comparable bacterial reduction across groups
Weiner et al. (2025), Israel [23]	First-in-human RCT, n=9	CF; nebulized BX004-A	Safe; effective lung delivery; bacterial load reduction
Wortelboer et al. (2023), Netherlands [24]	RCT, n=24	Metabolic syndrome; sterile fecal filtrate	Safe; phage composition altered; no metabolic improvement

Table 2 details the main characteristics of clinical cases in which phage therapy was used either on a compassionate basis or experimentally for the treatment of resistant bacterial infections. These studies indicate that the administration of phages either as monotherapy or in combination with antibiotics is a safe and clinically effective strategy for achieving microbial eradication or significant improvement in difficult-to-treat infections, such as those associated with cystic fibrosis, recurrent urinary tract infections, osteomyelitis, and mediastinitis. The versatility of the routes of administration (nebulization, local instillation, intravenous, and topical) and the ability of phages to induce microbiological and clinical improvements even against pan-resistant pathogens are noteworthy; however, in some cases bacterial resistance to phages has been observed, emphasizing the importance of developing personalized cocktails and combination therapies to minimize this risk and maximize the efficacy.

Table 2. *Characteristics of clinical cases.*

Author (year)	Clinical Context	Route	Main Outcome
Lebeaux et al. (2021) [25]	Lung transplant; pandrug-resistant *A. xylosoxidans*	Nebulized + instillation	Sustained eradication >2 years; no adverse events
Cook et al. (2025) [26]	Chronic ESBL UTI	Intravesical + oral + topical	Initial response; relapse; cure with ertapenem
Hameed et al. (2024) [27]	Pan-resistant mediastinitis	IV + local	Long-term resolution
Eskenazi et al. (2022) [28]	Fracture-related infection; XDR *K. pneumoniae*	Local + antibiotics	Clinical and radiological cure; confirmed synergy
Le et al. (2023) [29]	Post-transplant recurrent UTI	IV monotherapy	Sustained eradication at 1-year follow-up
Qin et al. (2021) [30]	Multifocal MDR UTI	Intravesical + nephrostomy	Cure after combined irrigation + antibiotics
Tan et al. (2021) [31]	CRAB lung infection	Nebulized	Pathogen clearance; clinical recovery
Van Nieuwenhuyse et al. (2022) [32]	XDR *P. aeruginosa* sepsis	IV + antibiotics	Bloodstream eradication; synergy demonstrated
Yang et al. (2025) [33]	CRPA pneumonia	Nebulized	Bacterial reduction; attenuated resistant strains
Li et al. (2025) [34]	Chronic biliary infection	Local PTCD	Partial response; resistance emergence controlled

Table 3 details the methodological characteristics and most relevant findings of four meta-analyses that analyzed the efficacy and safety of phage therapy in various clinical contexts. Although phage therapy has shown high effectiveness in historical contexts and in prosthetic joint infections, achieving success rates of up to 97% when combined with antibiotics, its efficacy in contemporary conditions such as urinary tract infections and pyoderma appears to be more variable, possibly due to the limited sample sizes and heterogeneity in study designs. Nevertheless, these studies highlight the promising potential of phage therapy as an alternative or

complement to antibiotics in multidrug-resistant infections.

Table 3. *Characteristics of meta-analyses.*

Author (year)	Scope / Sample	Key Findings
Liu et al. (2025) [35]	11 controlled studies (>200 patients)	51% infection eradication; no serious adverse events
Marongiu et al. (2022) [36]	21 trials (1921–2000+)	High historical efficacy; variable modern results
Meng et al. (2022) [37]	25 RCTs (9372 patients)	Eravacycline comparable/superior to tigecycline
Young et al. (2024) [38]	37 prosthetic joint cases	78% infection reduction; 97% success with combination therapy

4. Discussion

The findings of this review emphasize the potential of phage therapy as a viable and promising therapeutic option in the face of the growing crisis of antimicrobial resistance, with antibiotic options becoming increasingly limited. Randomized controlled trials have consistently reported the superiority of phage therapy compared with placebo or its equivalence with standard antibiotics; for example, in the case of chronic wounds, Karn et al. [17] observed 93.3% sterilization with phages, in contrast to 83.3% bacterial persistence in the placebo group. Similarly, in the context of cystic fibrosis, Kofi [20] and Weiner et al. [23] documented significant reductions in the burden of multidrug-resistant Pseudomonas aeruginosa and pulmonary improvement with the use of nebulized phages. These efficacy data are consistent with the conclusions of previous systematic reviews, such as those by Cocorullo et al. [14] for cystic fibrosis and Al-Anany et al. [15] for urinary tract infections, who also highlighted both clinical and microbiological improvements. The efficacy of phage therapy is generally increased when used in combination regimens with antibiotics. This was evident in Kofi's study [20], where combination therapy reduced the bacterial load by 67.2% (compared with 28.1% when using antibiotics alone), and in Krakhotkin's observational study [21] on recurrent cystitis, where the groups treated with phages combined with antibiotics showed more significant symptomatic improvements. These synergistic findings are supported by case studies such as that of Eskenazi et al. [28] for osteomyelitis and Van Nieuwenhuyse et al. [32] for sepsis, and are in line with the prospective study by Fedorov et al. [13], who reported a 12-fold reduction in relapses of prosthetic hip infection with combination therapy. Young's meta-analysis [38] on prosthetic joint infections further reinforces this claim, showing a 97% success rate with the combination treatment.

However, there is some heterogeneity in the reported results. Marongiu's meta-analysis [36] indicated that the efficacy reported in historical trials (1920s-1940s) for conditions such as dysentery was very high, while the evidence is more variable for contemporary conditions such as pyoderma possibly due to small sample sizes and methodological heterogeneity. This highlights the difference between early empirical use [9] and modern application, which requires standardization and rigorous design. One finding that was consistent across all studies reviewed randomized trials, clinical cases, and meta-analyses—is the favorable safety profile of phage therapy. No serious adverse events attributable to the administration of phages via topical, intravesical, intravenous, or nebulization routes were reported. The adverse effects reported were mild and transient, mainly associated with inflammatory reactions due to the release of bacterial endotoxins during lysis, as mentioned in the general results. This high tolerability validates the principle of phage host specificity, thus minimizing damage to the commensal microbiota, which represents a key advantage over broad-spectrum antibiotics. The safety observed in complex cases, including immunosuppressed or post-transplant patients as exemplified in the studies of Lebeaux et al. [25] and Van Nieuwenhuyse et al. [32] is particularly encouraging and supports the compassionate and experimental use of phage therapy. The similarities in efficacy and safety findings across different study designs and geographic regions reinforce the validity of this review, and the consistent superiority of combination therapy suggests a sound biological principle: phages can weaken biofilms and alter bacterial physiology, making cells more susceptible to antibiotics, while antibiotics can prevent or delay the development of phage resistance.

However, there are disagreements and limitations that require critical analysis: some clinical cases have reported complete success with intravenous phages alone, as indicated by Le et al. [29], while others, as in the case of Cook et al. [26], reported relapses after initial phage monotherapy, ultimately requiring an antibiotic to achieve a cure. These differences can be explained by several factors: first, biological factors the presence of polymicrobial or heterogeneous infections complicates the design of an effective phage cocktail [30]. Furthermore, the emergence of bacterial resistance to phages during treatment is a documented risk, as reported by Li et al. [34] and Yang et al. [33]. Curiously, in some cases, phage-resistant strains showed attenuated virulence [33]. Second, methodological factors most clinical cases are reports of compassionate use without a control group, which limits the possibility of generalization. In addition, the dose, frequency, route of administration, and customization of the phage cocktail are generally not standardized, introducing variability. Third, population-based factors—host characteristics (e.g., immune status), comorbidities (e.g., diabetes or COPD), and the type of infection (e.g., localized versus systemic, presence of foreign body) greatly influence the outcome. As Marongiu [36] has pointed out, the apparent greater efficacy in historical studies could be

attributed to publication bias, lack of rigorous controls, and the fact that they involved acute infections caused by strains that were possibly less complex than modern pan-resistant bacteria. Current methodological standards (PRISMA, double-blind RCT) are more demanding, which can make it difficult to demonstrate efficacy in small preliminary studies.

Limitations: As Al-Anany et al. [15] pointed out and as confirmed in this study the number of robust randomized longitudinal trials remains limited. Many of these trials have small sample sizes; for example, Nir-Paz et al. [18] included 19 participants, and Weiner et al. [23] included 9. Furthermore, the meta-analysis by Liu et al. [35], although recent, included a moderate number of patients.

Future research: This review positions phage therapy not as a substitute, but as a valuable addition to the therapeutic arsenal against multidrug-resistant infections. However, its integration into formal clinical practice requires overcoming regulatory and logistical challenges. Standardization in the production, purification, and characterization of phage preparations is essential. Likewise, algorithms are needed for the rapid selection of phages or customized cocktails, as well as a better understanding of the pharmacokinetics and pharmacodynamics of phages.

5. Conclusions

Phage therapy shows remarkable clinical and microbiological efficacy in the treatment of multidrug-resistant bacterial infections, especially in complex infections that are difficult to resolve such as chronic wounds, urinary tract infections, and those in patients with cystic fibrosis. The randomized controlled trials and clinical cases included in this systematic review consistently reported high rates of infection resolution, pathogen elimination, and clinical improvement in patients, positioning phage therapy as a powerful alternative in the advent of therapeutic failure of conventional antibiotics.

The safety of phage therapy is favorable and its tolerability is high, as evidenced by the findings of the included studies. No serious adverse events attributable to the administration of bacteriophages via various routes (topical, intravenous, or nebulization) were reported, validating its safe use in humans. This finding which was consistent throughout the reviewed literature supports the high specificity of phages toward their bacterial hosts, thus reinforcing the potential for their integration into therapeutic regimens to prevent concomitant damage to the beneficial host microbiota.

Furthermore, combination therapy, including both phages and antibiotics, is presented as the most robust and synergistic strategy, surpassing the results of either monotherapy. This review provides compelling evidence that such combinations not only enhance bacterial eradication and reduce biofilm formation but also decrease the emergence of resistance to both phages and antibiotics, thus addressing two of the main challenges in the treatment of multidrug-resistant infections.

Conflict of interest. The authors declare no conflicts of interest.

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