

Case Report

# Resolution of Chronic Bacterial Prostatitis with Bacteriophage-antibiotic Therapy

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## Summary

Chronic bacterial prostatitis is a commonly diagnosed genitourinary infection that presents significant challenges both in diagnosis and treatment. In an upcoming era of antibiotic resistance, and limited therapeutic options it becomes imperative to revise current guidelines and to provide more effective treatment strategies. At the Eliava Phage Therapy Center (Tbilisi, Georgia) we utilize bacteriophage therapy as an alternative approach against chronic bacterial infections. Bacteriophages, viruses that target and lyse specific bacterial cells, can be used as a stand-alone treatment or in conjunction with antibiotics. We present a case report of a patient with prostatitis caused by *Escherichia coli* infection, who prior to addressing our clinic, has been receiving antibiotic therapy without any positive effect. Our approach of combined use of antibiotics and phages was successful not only in complete clinical improvement but also in total bacterial eradication. This outcome shows the potential of bacteriophage therapy as a valuable adjunct to conventional antibacterials in the management of prostatitis.

## Introduction

Prostatitis, characterized by inflammation of the prostate gland, is a common condition with a lifetime prevalence rate of 1.8% to 8.2% [1]. According to the National Institutes of Health Classification, prostatitis is divided into the following categories: Acute bacterial prostatitis, Chronic Bacterial Prostatitis (CBP), Chronic non-bacterial prostatitis/Chronic pelvic pain syndrome, Inflammatory, Non-Inflammatory and Asymptomatic Inflammatory prostatitis [2]. Clinical manifestations mirror those of UTIs: increased urinary frequency, urgency, dysuria, discomfort in the pelvic area, abdominal discomfort, and low-grade fever [3]. Moreover, patients with CBP are usually diagnosed with recurrent urinary tract infections (UTIs) [4]. Interestingly, in some cases despite bacterial eradication, the symptoms still persevere [5]. This condition especially in the chronic form significantly alters the quality of life, affecting the mental and physical health of patients [6].

The main causative agents of CBP are *Enterococcus faecalis* and *Escherichia coli* [7]. It has been shown that *E. coli* caused acute prostatitis, and is associated with an increased biofilm formation [8], making it much more resistant to treatment.

Other possible causative pathogens include gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species, as well as atypical pathogens like *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Neisseria gonorrhoeae*, etc; [9]. Depending on the causative agent the treatment approach varies significantly.

Antibiotic therapy stands as the primary treatment for CBP, complemented by alpha-blockers, anti-inflammatory medications, hormonal treatment, lifestyle adjustments, and in some cases, surgical interventions [10]. Nonetheless, the recurrent nature of CBP and escalating antibiotic resistance rates among patients highlight the pressing need to study the spectrum of pathogens and antibiotic resistance rates [11]. Bacteriophage therapy (BT), used in conjunction with antibiotics or as a stand-alone treatment presents a promising alternative for combating CBP, as evidenced by studies conducted by Letkiewicz, et al. [12], Johri, et al. [13], Stevens, et al. [14], Leitner, et al. [15], and Gorski, et al. [16].

Bacteriophages, or phages are viruses that are abundant in the natural environment. They have the remarkable ability to infect and lyse the host bacteria. Each phage, a bacterial virus, is specialized to target a specific bacteria. Upon encountering

its target, a bacteriophage injects its genomic material, either DNA or RNA, into the bacterial cell, leading to its destruction. This group of viruses was introduced into clinical practice in the early 20<sup>th</sup> century, before the widespread use of antibiotic therapy.

Phage therapy has a long history of success in the treatment of infections in the Former Soviet Union Countries, where this group of viruses has been used as a mono-therapy, but also in some cases together with antibacterials. For today phage-antibiotic synergy is a promising approach to decrease the antibiotic resistance formation rate, biofilm penetration [17], and reduction of antibiotic dose intake [18].

At the Eliava Phage Therapy Center (EPTC) in Tbilisi, Georgia, we provide treatment to patients seeking BT for various chronic bacterial infections. The most common type of infection diagnosed at our clinic is the infection of the genitourinary system, including CBP. Drawing upon our clinic's extensive experience with this pathology, we used a combined approach of phages and antibiotics in the treatment of this patient. We achieved complete amelioration of chief complaints and eradication of the bacterial infection.

## Case report

In June 2023, a 65-year-old man sought treatment at the EPTC, where doctors confirmed the diagnosis of CBP. Upon presentation, his chief complaints included dysuria, increased urinary frequency, urinary urgency, and malodorous urine. Additionally, he reported experiencing high fever and extreme fatigue during acute infection episodes. Before his visit to EPTC, the patient has been on low-dose antibiotic therapy (Sulfamethoxazole and Trimethoprim) for five consecutive months, without experiencing any relief in his symptoms.

The patient was first diagnosed with CBP in April of 2022. He received emergency care in the US due to spiking fever, chills, body aches, numbness of fingers, and chest pain. The infection was attributed to *Escherichia coli* ( $>1.10^5$ CFU/mL), characterized by ESBL (Extended Spectrum Beta-Lactamase) and MDR (Multi-Drug-Resistant Organisms). The patient was administered IV Fosfomycin initially, but he experienced a severe adverse reaction to the medication. Consequently, he was switched to Bactrim (Sulfamethoxazole and Trimethoprim) for a duration of 6 weeks.

Before the hospitalization, the patient experienced a gradual decline in health over 8 weeks, during which the bacterial urine culture consistently showed negative results. Since then, he has experienced multiple episodes of acute bacterial infection, which has eventually become chronic in nature. The urine culture test remained positive for *E. coli* infection (Table 1). He received therapy with multiple antibiotics including Sulfamethoxazole and Trimethoprim, Fosfomycin, Penicillin, and Levofloxacin. The duration of time off of antibiotic therapy was gradually shortened, to the

**Table 1:** Results of urine bacterial culture tests conducted in the US before the initiation of BT.

Date	Urine Culture Test Results
08.04.2022	<i>Escherichia coli</i> $>1.10^5$ CFU/mL
10.05.2022	<i>Escherichia coli</i> $>1.10^5$ CFU/mL
10.10.2022	Negative: No growth
22.12.2022	<i>Escherichia coli</i> $>1.10^5$ CFU/mL
17.02.2023	<i>Escherichia coli</i> $>1.10^5$ CFU/mL

point the patient discontinued therapy; he noticed symptoms returning within 2-3 days.

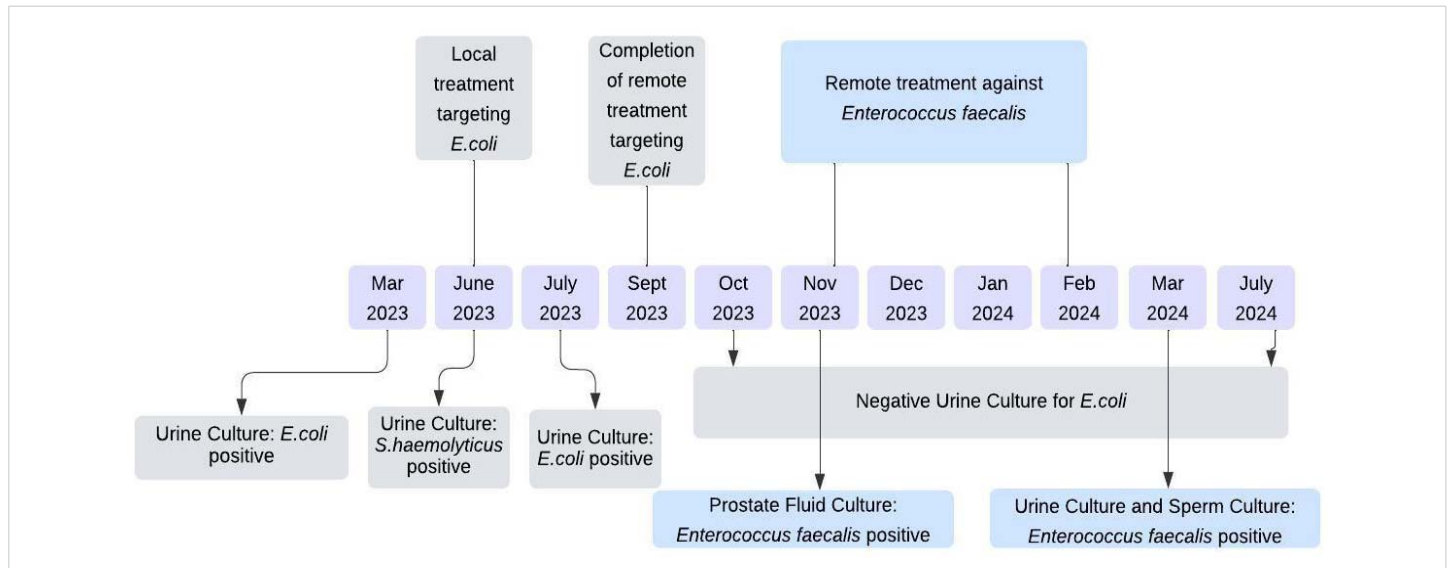
The patient's past medical history is significant for extensive antibiotic use and complicated surgeries, including perforated colon repair surgery in 2018, followed by two hernia repair surgeries and a shoulder replacement surgery. In July 2021, he was hospitalized due to abdominal obstruction. According to the patient, his genitourinary problems have slowly started, following this hospitalization. It is also worth noting that at 28 years old, he has undergone extensive IV antibiotic therapy, which was necessitated by a lacerated liver.

The urine culture tests conducted at the Eliava Analytic-Diagnostic Center in March of 2023, also confirmed an *E. coli* infection with a count of  $>1.10^4$  CFU/mL. Additionally, a sperm culture showed the presence of *E. coli*  $>5.10^6$  CFU/mL. The bacterial strain isolated from the urine revealed resistance to commercially available, phage preparations with fixed composition: Pyo phage, Intesti phage, Ses phage, and Enko phage. Therefore, the decision was made to develop a custom phage by the G. Eliava Institute of Bacteriophages, Microbiology, and Virology, using the patient's specific bacterial strain.

Local treatment was administered with customized phage at the EPTC from June 9 to June 23, 2023 (Figure 1). During this period, the urine culture test revealed *Staphylococcus haemolyticus* at a count of  $3 \times 10^3$  CFU/mL, which exhibited sensitivity to Pyo phage, intermediate sensitivity to Intesti, Fersis, Ses, and Enko phage. The sperm culture test remained negative at this time. Based on the sensitivity testing a decision was made to pursue the following combination therapy:

1. Pyo bacteriophage: 10 mL orally in the morning.
2. *E. coli* custom bacteriophage: 10 mL orally in the evening.
3. Ses bacteriophage: rectal suppository once a day.
4. Bactrim antibiotic: 160 mg twice a day. (The dosage and frequency remained unchanged since starting the phage treatment).

The therapy was given for 35 consecutive days followed by a ten-day break. The next two rounds of BT were administered over a period of 20 days, with again a ten-day break in between. After the first round of BT, a urine culture test was



**Figure 1:** The timeline of treatment involves both ready-to-use phages, as well as custom-made phage preparations.

repeated in the US, which revealed a bacterial count up to  $2.5 \times 10^4$  CFU/mL. Following the completion of BT, subsequent urine culture tests were performed seven times and returned negative results.

Throughout the treatment process, we also monitored the bacterial load in sperm ejaculate and prostate fluid. In November 2023, the prostate fluid culture revealed *Enterococcus faecalis*  $>5.10^5$  CFU/mL. This month, without prior sensitivity testing, the decision was made to initiate Intesti phage therapy in combination with Levaquin. Intesti phage that includes active phage against *Enterococcus* was shipped to the US and the patient was provided with the following instructions: 10mL in the morning and 10 mL in the evening *per os* for 20 days, with a 15-day break between each curative period. This cycle was repeated three times. Tests performed in March at the Eliava diagnostic center revealed an *E.faecalis* sperm count of  $5.10^3$  and a urine culture test count of less than  $1.10^3$  CFU/mL.

The decrease in urinary bacterial load coincided with the improvement of the patient's clinical complaints. By the middle of the last 20-day period of BT targeting an *E.coli* infection, there was a notable enhancement in the patient's well-being. As of July 2024, he continues to remain symptom-free. No allergic reactions or adverse effects were documented throughout the phage therapy.

## Discussion

While prostate fluid analysis is valuable in CBP assessment, urine culture tests are more accessible for patients, and remain mandatory for the diagnosis [19]. Consequently, our evaluation of the patient's health condition primarily relied on urine culture tests, supplemented by a couple of semen culture tests conducted in parallel. Even though the value of semen culture tests has been challenged in prostatitis,

a study has also found a correlation between prostate and semen culture tests [20]. From our findings, we identified *E. coli* as the main cause of infection. The reduction in bacterial load aligned with the amelioration of the clinical symptoms. It is worth emphasizing that our analysis relied on lab tests performed locally at Eliava Diagnostic Center and patient-reported results from the US. Importantly, the findings from both laboratories were consistent with each other.

Since the patient was receiving a combination therapy of antibiotics and phages, it is hard to attribute improvements to one treatment over the other. However, it is clear that the use of Bactrim antibiotic alone did not yield clinical improvement for months, and only combination therapy - antibiotic with bacteriophage proved effective in achieving positive results. This shows the potential of phage and antibiotic synergy, which has been described by multiple authors [21,22]. *In vitro* studies have demonstrated positive synergetic effects against MDR uropathogenic *E.coli* [23].

The formation of bacterial biofilms presents a significant challenge to the effectiveness of antibiotics, particularly in cases where *E. coli* is a well-known contributor to biofilm production [24]. Although antibiotics are typically the primary treatment for CBP [9], their efficacy can be limited, especially in cases of refractory infections, necessitating a switch to different antibiotic classes. Biofilm formation by various etiological agents such as *Staphylococcus* spp, *Enterococcus* spp, *E. coli*, *Enterobacteriaceae*, and *Pseudomonas aeruginosa* is common [25]. Considering this challenge, the combined use of phage therapy and antibiotics could offer a viable option for the treatment of CBP, as phages and phage-encoded enzymes have been shown as potential agents for biofilm penetration [26]. Moreover, the combination use of phages and antibiotics is promising against not only biofilm penetration but also for decreasing the risk of phage resistance development [27]. Our case report is another example, that showcases the

importance of using phages in cases where there is severe resistance against antibiotics alone, possibly due to biofilm formation.

The human bladder was once considered a sterile environment, but this myth has since been debunked by various studies [28,29]. It has been shown that the urinary microbiome plays a key role in the maintenance of overall urinary health and differs in “healthy” patients vs. those with genitourinary infections [30]. Phages, along with other microorganisms such as bacteria, fungi, and protozoa form the human bladder microbiome [31]. Thus, the urinary microbiome is sustained by a delicate balance between pathogenic and non-pathogenic bacteria. Disruptions to this balance can occur when the composition of organisms changes. During a bacterial infection, specific phages target and kill the infectious agent - host bacteria while simultaneously helping to restore the microbial equilibrium. In nature, phages and bacteria engage in continuous co-evolutionary processes. Introducing exogenous phage preparations into the urinary microbiome can positively impact this balance by reducing the number of pathogenic bacteria and thereby promoting the proliferation of beneficial bacteria.

Phage therapy has been widely utilized in clinical practice in Georgia for decades. At Eliava Phage Therapy Center, we employ phage preparations to combat infectious diseases affecting various organ systems. In recent years there has been a marked interest in BT, as evidenced by a growing number of registered clinical trials and an expanding number of institutions practicing phage therapy. Based on the results of double-blind studies, phage preparations could potentially have broader applications in the future, challenging the current status quo of antibiotics.

The treatment of infectious diseases using various antibacterial solutions, including phages, is approximately comparable from a financial perspective. However, phage therapy necessitates experienced scientists for the selection and development of specific, high-quality phage preparations, which can be a costly process and, for now, is only conducted by a couple of Institutions, such as the Eliava Institute. If the isolated bacterial strain is sensitive to an already developed and commercially available phage preparation, the costs associated with phage therapy can be nearly equivalent to conventional treatment of infectious complications.

## Conclusion

Emerging antibiotic resistance poses a significant challenge in the treatment of chronic bacterial infections. We used a combination of antibiotics and bacteriophage preparations for treating chronic bacterial prostatitis and achieved both complete clinical improvement and eradication of *E. coli*-caused infection. We believe this case report once again demonstrates the effectiveness of synergetic treatment against chronic urogenital infections.

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