GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 5 (374) Май 2026

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
NO 5 (374) 2026

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EARLY HUMORAL IMMUNE RESPONSES TO BACTERIOPHAGES AND SHORT-COURSE PHAGE THERAPY OUTCOMES IN PATIENTS WITH URINARY TRACT INFECTIONS

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Abstract.

Urinary tract infections (UTIs) cause significant morbidity in the adult population. Increased drug resistance and biofilm formation by uropathogenic bacteria make their eradication difficult. Phage therapy (PT), especially using custom-made preparations, is regarded as a valuable alternative treatment with promising results. The PT outcome is highly dependent on the appropriate selection of candidate phages for therapeutic mixtures and the effective routes and duration of administration. However, activation of the body's immune mechanisms through phage administration could play a negative role. A number of studies have shown the presence of antiphage antibodies (APA) in the sera of phage-treated patients, but their presence in other biological fluids still remain unclear. We studied the early antibody responses in 11 patients with persistent UTIs treated at the Eliava Phage Therapy Center (EPTC) with custom or commercial phage preparations administered orally, rectally, vaginally, intravesically, or in combined modes. PT efficacy was monitored clinically and bacteriologically. APAs in serum, urine, and saliva were measured by neutralization assay and ELISA before therapy, on day 7, and day 14. Natural APA levels were measured in 6 healthy volunteers as well. Low baseline APA levels were detected in both patients and healthy subjects. During PT, in most patients increasing APA responses were detected in serum, and to a lesser extent in urine and saliva. No significant influence of APA levels on PT outcome during short-term treatment was found.

Key words. Urinary tract infections, phage therapy.

Introduction.

Urinary tract infections (UTIs), manifested mainly as urethritis, cystitis, and pyelonephritis, cause substantial morbidity in both men and women, with an estimated 150 million cases annually worldwide, significantly reducing their quality of life [1,2]. In healthy adult individuals, especially in almost 50% females, UTIs are typically acute and uncomplicated. Complicated UTIs frequently develop in catheterized females in the post-operational period, male patients with prostatitis or those with urinary tract dysfunction. Those conditions often become chronic with recurrent episodes and with potentially severe consequences such as sepsis, meningitis, or renal failure [1,3].

UTIs are caused by various uropathogens, most commonly *Escherichia coli*, followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus saprophyticus* and some other coagulase negative (CoN) staphylococci, *S. aureus, Pseudomonas aeruginosa*, group B streptococci, *Enterobacter spp*., *Enterococcus* spp. Increasing antibiotic resistance, extracellular matrix and biofilm formation by uropathogenic bacteria contribute to evading host defenses and significantly complicate treatment efficacy of patients with UTIs [1-4]. Alternative or complementary strategy based on application of biological means, such as bacterial vaccines/lysates, small compounds, nutraceuticals, immunomodulating agents, probiotics and bacteriophages, are more intensively suggested for medical practice [4,5].

Bacteriophages (phages) comprise a major natural component of the human microbiome. They inhabit many organ systems, cross epithelial barriers, and shape bacterial community structures. Phages can interact with and affect the mammalian immune system through the interaction with bacterial microbiome and also directly - via cellular uptake and recognition of phages [6]. Bacteriophage adherence to mucus layers provides a ubiquitous, non–host-derived, immunity serving as barrier to bacterial invasion [7]. Diverse phage populations in the gastrointestinal and respiratory tracts highlight their role in maintaining host homeostasis [8]. The bladder-associated phages also may contribute to urinary health although the urinary phageome is relatively less studied [9,10].

Phage therapy is increasingly recognized as a promising alternative for antibiotic-resistant infections [11]. In Georgia and other former Soviet countries, therapeutic bacteriophages have been used for decades for prevention and treatment of various human bacterial infections [12-14]. Renewed interest in phages and PT in the fight against AMR has led to growing global adoption in Western countries. PT has been applied to many bacterial infections, including UTIs. The controlled clinical trials conducted in Georgia demonstrated its safety and comparable efficacy to antibiotics [15,16].

Successful PT depends on the availability of specific phages, their appropriate selection, effective administration strategies and also on immune responses, particularly production of anti-phage antibodies (APA) which may influence therapeutic outcomes. Phages induce the T-dependent type of immune response, including anti-phage humoral response, similar to that induced by many other antigens [17,18]. Phages may initiate both - innate immunity (phagocytosis, cytokine responses) and adaptive immunity (antibody production) responses [6,19]. Cross-reactive antibodies against therapeutic phages have been detected in both patients and healthy individuals prior to phage

administration, likely reflecting prior environmental exposure to bacteriophages [20,21]. APA development follows classical humoral kinetics: early IgM peaks and increased IgG levels around days 20–21 post-exposure. Individual immune status, comorbidities, and previous treatments may influence APA dynamics.

Neutralizing antibodies may reduce circulating phage levels and diminish therapeutic efficacy [22,23]. However, a number of studies have indicated that increased APA levels do not consistently correlate with PT failure, and in general, there is no consensus to date regarding whether phage-specific antibodies affect the clinical outcomes of phage therapy [24,25].

The aim of this prospective observational case-based study was to evaluate efficacy of short-term PT in patients with UTIs treated at the EPTC and to determine the APA levels against therapeutic phages in serum, urine, and saliva of patients before, during, and after the phage treatment.

Materials and Methods.

Selection of patients and healthy volunteers:

The study included selected adult patients admitted to the Eliava Phage Therapy Center (EPTC) between May 2022 and June 2023. Eleven patients aged 25 to 85 years, of different nationalities and with persistent or recurrent chronic urinary tract infections (UTIs), were included in the study. For each patient, a comprehensive clinical file was compiled, including medical history, presenting symptoms, instrumental examinations, microbiological findings, and treatment protocols. Patients received either custom-made phage preparations (or autophages) and/or commercial bacteriophage mixtures administered via oral, rectal, vaginal, intravesical, or combined routes. Six healthy individuals (3 males and 3 females, aged 22–60) without urinary tract disturbances or other evidence of infection were also included in the study for comparison, not as a control group, but to determine baseline levels of naturally occurring APAs.

Ethics approval:

The study was approved by the Bioethics Committee of the G. Eliava Institute of Bacteriophages, Microbiology and Virology (approval #2022/03). All procedures were performed in accordance with the Declaration of Helsinki and national regulations governing clinical phage therapy. In addition to the standard written informed consent signed by each patient upon admission to the EPTC, all enrolled patients were informed about the use of their biological samples and clinical data in the research.

Clinical and laboratory evaluation:

Diagnostic assessments of enrolled patients were performed at the Eliava Phage Therapy Center (EPTC). Clinical evaluation included the patient's history, general physical examination, and, when clinically indicated, abdominal ultrasonography or computed tomography. Clinical -laboratory analyses, conducted at the Eliava Analytical-Diagnostic Center (EADC), included complete blood count, urinalysis, C-reactive protein (CRP), coagulation profile, serum glucose, and evaluation of thyroid, liver, and kidney functions.

Biological sample collection and processing:

Blood samples (5–10ml) were collected into gel and clot-activator tubes, centrifuged at 2000g for 15 minutes, and the resulting serum aliquots were stored at −80°C. Urine samples were collected in sterile containers, centrifuged at 1500g for 10 min, and concentrated approximately 100-fold using 30 kDa Amicon Ultra centrifugal filters (Merck, Millipore). The protein concentration was measured before and after concentration. Saliva samples were collected with the addition of EDTA, centrifuged at 1500 g 15 min, and in some cases further concentrated using 30kDa Amicon Ultra filters. All specimens were stored at −80°C until used for APA measurements.

Bacteriological analysis:

Bacteriological analysis of biological samples (urine, vaginal and urethral swabs, semen, prostate secretion, saliva) was performed following standard microbiological protocols [26]. Microbiological testing and enumeration employed standard techniques - plating of liquid samples, primarily urine, or four-quadrant streaking for vaginal and urethral swabs on relevant microbiological media. Bacterial counts were reported as a number of colony forming units per mL (cfu/ml). Colony counts yielding $\geq 10^5$ cfu/ml of urine was indicative of significant bacteriuria, while $\geq 10^3$ cfu/ml of a single uropathogen was considered sufficient for diagnostics of UTIs in symptomatic chronic patients. The leading bacterial isolates were characterized by basic biochemical-cultural properties and identified using the automated VITEK 2 system (BioMérieux, France).

For the bacteriological assessment of treatment outcomes, the following thresholds were defined: "significant reduction" as a ≥3 log decrease in cfu/ml, "low to moderate reduction" as a 1–2 log decrease, "eradication" as no detectable bacterial growth and "no response" as <1 log change or stable counts.

Therapeutic phage preparations used in PT and supplementary treatments:

Commercial bacteriophage preparations produced by Eliava "Biopreparations Ltd", Georgia, were used, including cocktails - Intestiphage, Pyophage, SES bacteriophage, Enko bacteriophage, and a monophage -Staphylococcal phage. Each of these sterile-filtered phage lysates contain active virulent phages at concentrations 10^5 - 10^6 PFU/mL. Depending on physicians' prescription, phages were administered orally, rectally, vaginally or intravesically. The custom phages for personalized treatment were ordered to the Eliava Authorized Pharmacy (EAP) and were prepared in the labs of the Eliava Institute by standard techniques for phage isolation, propagation and selection [27,28] using particular bacterial isolates from individual patients (strains of *E. faecalis, P. aeruginosa, K. pneumoniae, E. cloacae* etc).

Some patients, in their best interest, received adjunctive therapies based on the use of biological preparations such as: i) "Enteroflorid", (Biopharm, Georgia) containing $\geq 10^8$ live probiotic microbes, predominantly lactic acid bacteria; ii) "Urostim" (GM Pharma, Georgia) - an immunostimulant, composed of lyophilized killed cultures from of *E. coli, P. proteus, E. faecalis, K. pneumoniae*; iii) "Sanuren" (Orlando Medicine, Italy) -an anti-inflammatory herbal formulation for

UTIs. In single cases oral antibiotics were used in combined antimicrobial therapy.

Processing of phage antigens for APA assays:

Phage suspensions, used as antigens for assessing anti phage antibodies (APA), were derived and processed from autophage preparations and /or commercial phage cocktails showing high lytic activity against patients' bacterial strains. High titer phage lysates ($\geq 10^{10}$ PFU/ml) were obtained via propagation on liquid and solid semi-synthetic media by standard methodology [27-29]. After high-speed centrifugation (18000–20000 rpm, 1-1.5 hr) phage pellets were resuspended in SM buffer and stored at 4°C overnight, then centrifuged at 5000 rpm 20 min and supernatant dialyzed against PBS for 24 hours. The obtained semi-purified phage preparations were checked for final titer and tested for Endotoxin content using the ToxinSensor™ Chromogenic LAL Endotoxin Assay Kit (Gen Script, USA) according to the manufacturer's instructions. Phage preparations were stored at 4°C until used in immunological assays.

Neutralization assay for APA detection:

Anti phage neutralizing activity in biological samples was determined using classical methodology [27,28]. Briefly, serum, urine, and saliva samples were diluted in saline (1:25, 1:50, 1:100, 1:200) and incubated with phage suspensions for predefined time intervals (10 and 30 minutes). The quantity of infective phage particles before and after incubation was measured by double layer method to calculate percent of inactivated phages. The neutralization constant K was determined using the formula: $K = 2.3 \times (D/T) \times \log(P_0/Pt)$ where, K is the rate of phage inactivation, D - serum dilution, T - the time of reaction in minutes (10 and 30 min), $P0$ -the initial phage titer and Pt - the phage titer after reaction. K values ≤5 were interpreted as a weak neutralization [24,30].

Detection and quantification of APAs by ELISA:

The indirect ELISA was used to measure APAs in blood sera, saliva and urine according to a number of protocols [21,22,24,29] with some modifications. Briefly, the samples of semi purified phage preparations ($1x10^8$pfu/ml) were adsorbed onto 96 flat-bottom well plates, incubated for 1 hr at 37°C and kept overnight at 4°C. After 5x washing with 1xPBS the blocking solution - 2% Bovine serum albumin (BSA)- was added and incubated at room temperature for 2hrs. Then the processed samples of sera, urine and saliva diluted across a range of 1:25–1:800 (mostly standardized at 1:50) were added and incubated for 2 hrs at 37°C. After multiple washings secondary antibodies- HRP conjugated total anti human IgG/A/M antibodies (Novex, Life Technologies, USA) at the dilution 1:2500 were added and incubated for 1hr at 37°C. Following a series of washings a substrate -Ultra- TMB-ELISA (Thermoscientific, USA) was added, according to the manufacturer's instructions. After stopping the reaction with 0.2 M H_2SO_4, the absorbance of ELISA plates was measured at 450 nm on the microplate reader EL808 (Biotek, USA). The absorbance values for control samples (without phage) were subtracted.

Comparison of average APA levels:

To contrast the changes in APA levels between samples arithmetic means were calculated on the values obtained from all patients (n = 11) and the box plots were constructed. For each average the coefficient of variance (CV) was also measured. To assess changes over time within the same patient group, the non-parametric Wilcoxon matched-pairs signed rank test was used to compare Day 0 against Day 7 and Day 14 separately for each sample type (serum, urine, and saliva). Baseline APA levels for patients (Day 0, n = 11) compared to that of healthy individuals (n = 6) were expressed as ratios. Statistical significance for these independent groups was determined using the Mann-Whitney U test. All significances were calculated in GraphPad Prism 8.

Results and Discussion.

Phage therapy of patients with UTIs: Case reports.

The eleven case reports (CR), with a brief description of patient's health status, causative agents and the treatment undertaken in the frames of this observational study are given below.

CR #1. An 85-year-old female from France had a more than 10-year history of recurrent urinary tract infections treated with multiple courses of antibiotics without stable improvement. She visited the EPTC twice with >3 years interval. At first admission she was treated with phage preparations for bacterial vaginitis and chronic cystitis that gave her nearly three years of remission until she was hospitalized because of worsened UTI symptoms. Since antibiotic therapy courses were unsuccessful, the patient returned to the EPTC. Microbiological examination revealed *S. aureus* (10^6 cfu/ml), *E. coli* (10^4 cfu/ml), and *E faecalis* (10^5 cfu/ml) in urine and vaginal smears. Treatment consisted of SES bacteriophage, Intestiphage, and Pyophage administered orally twice daily and as vaginal suppositories once daily. During 18 days, her symptoms were resolved gradually and urine samples showed bacterial counts reduced by 2-3 log. Six months later she experienced a recurrence caused by *E. coli*, which responded well to home treatment with commercial Eliava phages.

CR #2. A 25-year-old male from the United States had chronic prostatitis for several years, unresponsive to antibiotic therapy. He contacted the EPTC remotely and sent his specimens for bacteriology. Semen culture revealed *E. cloacae* (10^6 cfu/ml), and the autophage was prepared. Upon admission at the EPTC he reported dysuria and pelvic pain. Cultures showed *E. cloacae, S. capitis*, and *S. hominis*. Treatment included *E. cloacae* autophage, Pyophage and Intestiphage administered orally and rectally, and the probiotic Enteroflorid. During the patient's stay at the EPTC his symptoms improved moderately; *E. cloacae* counts were moderately reduced though *S. capitis* persisted. Two further courses of phage therapy with Eliava phages at home resulted in satisfactory health status of the patient.

CR #3. A 36-year-old female from the United Kingdom had a 15-year history of genitourinary problems, which worsened with urethral burning and vaginal discharge several months before application to the EPTC. Remote microbiological analysis revealed *Enterococcus faecalis*, and a customized phage was prepared. Clinical -laboratory investigations at the EPTC diagnosed bacterial vaginitis and chronic cystitis, with *E. faecalis* and *Staphylococcus hominis* isolated. Treatment included *E. faecalis* autophage, Intestiphage, and Staphphage given orally and vaginally. After two weeks, her symptoms

decreased markedly, accompanied by 3 log reduction of *E. faecalis* counts. At the three months follow up, a further decrease in bacterial counts was documented, and by six months she reported complete clinical recovery.

CR #4. A 34-year-old male from the United States had a three-year history of prostatitis following a sexual encounter. He reported frequent urination, genital discomfort, and suprapubic pain. A urine and prostate secretion culture revealed *S. hominis* (10^4 -10^5 cfu/ml). Upon admission to the EPTC, treatment consisted of oral Intestiphage and SES bacteriophage administered twice daily, rectal SES suppositories, and Enteroflorid. Symptoms improved considerably, and *S. hominis* counts decreased by 2log. The patient remained stable for three months following treatment.

CR #5. A 33-year-old male from Southeast Asia suffered from bacterial prostatitis for three years, characterized by pelvic pain, urinary discomfort, and reduced libido. Initial cultures revealed *E. faecalis*. Despite antibiotic therapy, symptoms persisted. Upon admission to the EPTC, cultures from urine, semen, and prostate secretion showed *E. faecalis* (10^5 cfu/ml) and *S. haemolyticus* (10^4 cfu/ml). Combined treatment included oral and rectal Intestiphage, antibiotic Amoxiclav, subsequently an autophage of *E. faecalis* was added. After a 17-day course, his symptoms improved markedly accompanied by 3- 3,5 log reduction of bacterial load. The patient continued treatment with the Eliava phages at home. *E. faecalis* was eradicated. No serious infectious episodes were reported at the eight months follow up.

CR #6. A 51-year-old male from India had chronic urinary infection for several years, with recurrent episodes of dysuria and perineal pain. Previously isolated *E. faecalis* prompted preparation of an autophage. Upon admission to the EPTC, moderate to high quantities of *E. faecalis* (10^6 cfu/ml) and *S. epidermidis* (10^4 cfu/ml) were detected. Treatment included oral *E. faecalis* autophage and Intestiphage, and seven sessions of urethral instillation of Intestiphage. By discharge, the patient's symptoms had improved significantly, and the cultures were negative for the target pathogens.

CR #7. A 43-year-old female from Germany had a decade long history of bilateral pyelonephritis with recurrent hospitalizations and multiple intravenous antibiotic courses. She applied to the EPTC, sent her urine culture in which *K. pneumoniae* was revealed and the autophage was prepared. Upon admission to the EPTC she reported flank pain and weakness. The results of an ultrasound scan indicated kidney stones and residual urine. Cultures showed *K. pneumoniae* (10^6cfu/ml), *Streptococcus agalactiae* (10^5cfu/ml), and *S. aureus* (10^4 cfu/ml). Treatment consisted of *K. pneumoniae* autophage administered orally and vaginally, and Intestiphage orally. After 13 days treatment practically no improvement in patient's subjective feelings was observed, and bacterial counts did not decrease as well. No follow up information was obtained after discharge of the patient from the EPTC.

CR #8. A 72-year-old male from Australia developed chronic UTIs following bladder surgery requiring regular treatment. Six years later, after catheterization he acquired *Pseudomonas aeruginosa* infection. The specimen sent to the EPTC showed a high microbial load (10^8cfu/ml) and a customized *P. aeruginosa* phage was prepared. Several months later, upon admission to the EPTC he exhibited moderate levels of *P. aeruginosa*, *S. epidermidis*, and *E. faecalis*. Treatment began with bladder lavage and a single intravesical instillation with Intestiphage, followed by a 15 days course of oral and rectal *P. aeruginosa* autophage, also oral Intestiphage, Pyophage, and Enkophage. The patient's condition remained stable, with improved subjective feelings although only moderate bacterial reduction (by 2 log) was achieved. Over the following year he reported occasional symptom exacerbations that were manageable at home by application of Eliava commercial phages.

CR #9. A 28-year-old male from China suffered lower abdominal and genital pain for 2 years before applying to the EPTC. Multiple antibiotic courses were ineffective. Upon admission he was diagnosed with chronic UTI, with high counts (10^6 cfu/ml) of *E. faecalis* and *S. aureus* in urine and semen. Combined treatment with oral Intestiphage and Pyophage, rectal Intestiphage suppositories, and Urostim resulted in significant symptomatic improvement. *S. aureus* was eradicated and *E. faecalis* counts decreased significantly. Four months follow up confirmed the absence of *E. faecalis*. After 18 months a recurrence due to *E. cloacae* was successfully treated with the autophage, newly prepared and sent by Eliava Authorized Pharmacy (EAP).

CR #10. A 29-year-old female from the United Kingdom had persistent dysuria, urinary frequency, and pelvic discomfort for about 3 years. *E. coli* was repeatedly detected. Multiple courses of intravenous antibiotics provided only temporary relief. Upon admission to the EPTC she was diagnosed with chronic cystitis and bacterial vaginitis. Urine and vaginal cultures revealed *E. coli* (10^6 cfu/ml), *E. faecalis* (10^6 cfu/ml), and *S. haemolyticus* (10^5 cfu/ml). Combined treatment included oral Intestiphage and SES bacteriophage, Intestiphage vaginal suppositories, Urostim, and Sanuren. After 17 days, her symptoms improved significantly and bacterial counts decreased to 10^2 -10^3 cfu/ml. The PT course continued at home with commercial Eliava phages that resulted in eradication of both *E. coli* and *E. faecalis*, with intermittent low-level *S. haemolyticus* that wasn't considered clinically significant.

CR #11. A 68-year-old female from France had chronic urinary symptoms including frequent urination, burning, foul smelling urine, vaginal discharge, and constipation. Microbiological testing of urine, vaginal and urethral swabs revealed *E. faecalis* (10^5 cfu/ml) and moderate load of *S. haemolyticus*. Combined treatment with oral Intestiphage and Pyophage, Intestiphage vaginal suppositories, also Urostim, Enteroflorid, and Sanuren resulted in marked clinical improvement. At discharge, cultures were negative for previously isolated uropathogens. The patient continued treatment with commercial phages at home, without further recurrence during following 6 months.

The presented 11 case reports on patients with UTIs who underwent short- course phage treatment at the EPTC showed a quite diverse clinical picture – in terms of the patients' initial status, disease duration and severity, the treatment regimen used and also the outcomes. The clinical assessments of all patients before PT course, as well as clinical-laboratory testing results (not presented here) corresponded to the characteristics of chronic diseases with long-term history. As to previous

experience with PT, only one patient (#1, an 85-year-old female) has been treated with Eliava commercial phages orally three years prior to the current study; all other patients were phage-naïve.

Determining the causative agents of UTIs is the most important part of the treatment strategy. The bacteriological analysis of patients' biological samples before treatment initiation revealed the presence of some anticipated bacterial species, commonly causing inflammatory processes in the UT. Most frequently and in significant quantities (10^5 -10^6 cfu/ml) *E. faecalis* was encountered (in 6 patients), followed by *E. coli* (2 patients), *K. pneumoniae* and *E. cloacae* (in single patients each). It has to be noted that various *Staphylococcus* species (*S. aureus, S. hominis, S. haemolyticus, S. epidermidis*) were found in the majority of patients, although not always in etiologically significant amounts. Regarding antibiotic resistance, in part of the patients bacterial isolates showed still certain susceptibility to a number of antibiotics, while several other patients were colonized with bacteria resistant to several antibiotics simultaneously (data not shown).

The treatment of patients was carried out by commercial phages and, in some cases, additionally with autophages, administered orally (per os) as well as via rectal or vaginal suppositories. Additional procedures, such as intravesical phage instillations, were performed in two patients only: patient #6 (7 series of instillations) and patient #8 (a single instillation following bladder lavage, upon admission). While it is recognized that different routes of administration may influence therapeutic outcomes as well as the associated immune responses, the limited sample size in our study does not allow for a meaningful assessment of these variables.

To analyze the outcomes of phage therapy in a group of selected UTI patients in relation to immune response, particularly APA levels we firstly assessed the treatment effectiveness and categorized them using an approach quite similar to that of previous studies [24,30]. The evaluation of treatment outcomes of the study patients with UTIs was based on microbiological findings, medical examinations, clinical laboratory indicators, as well as the patient's subjective symptoms and overall health status after completing a short course of PT (14 days in average) at the EPTC. For some patients, certain feedback information was also available (see case reports). The categorization of the 11 study patients is presented in Table 1. The description of categories is given under the table.

The brief analysis of the case reports revealed a quite good overall outcome in the study group: 10 out of the 11 chronically ill patients completed the treatment course at the EPTC with positive outcomes (categories A, B, and C). Among them 6 patients demonstrated good clinical results with eradication or significant reduction of pathogens (3 patients of A and B categories each). In the C category with 4 patients, clinical stabilization and improved overall health status was registered but without satisfactory laboratory findings. For one female patient -with severe chronic long-term pyelonephritis - 14 days treatment didn't yield in improvement of health status by both objective criteria and subjective symptoms (category D-E). We assume that the PT outcome in this particular patient could have been significantly improved if purified phage preparations had been administered parenterally, primarily via the intravenous route, which was not available at the EPTC.

The main aim of our study was to investigate the immune response in patients in the course of phage therapy conducted at the EPTC, in particular to measure the APA development and to compare obtained data with the clinical outcomes in study patients.

Assessment of antiphage antibody (APA) levels in patients with UTIs.

In all eleven patients studied the APA levels and their dynamics were determined in serum, urine, and saliva samples collected before treatment (day 0) and on days 7 and 14 following PT initiation. In total, 99 samples from patients have been used in immune assays. In our research, two types of phages were used for measuring APAs in biological samples: i) custom phages - specifically prepared using patient's own bacterial isolates; ii) mixture of phages isolated from the commercial cocktail "Intestiphage"(used in the treatment of practically all patients in the study group) by cloning and propagating on the host strains of *S. aureus, E. coli, P. aeruginosa* and *E. feacalis*. Both types of phages underwent a procedure for obtaining semi-purified phage (see section "Materials and methods'). Two complementary methodologies – the phage neutralization assay and the ELISA - were used to assess APA levels in patients' samples. For comparison the APAs were quantified in biological fluids from six randomly selected healthy individuals without symptoms and bacteriological indication of UTIs.

Importantly to note from the beginning that APA levels in biological fluids from all 11 study patients were measured against four phage components derived from the Intestiphage commercial preparation, and the resulting data are presented below (Figure 1 and 2). Intestiphage derived phages were selected as antigens because all patients in the study received Intestiphage as part of their treatment, regardless of whether they also received autophages or other commercial preparations. This allowed us to use a standardized antigen source across all participants, ensuring methodological consistency in APA measurements. As to bespoke phages, that have been used in PT of 5 patients (in parallel with the Intestiphage application), the results of APA measurements will be published later separately, together with data for other patients treated with custom-made phages, once the corresponding cohorts reach a sufficient size. We can only briefly note here that levels and dynamics of APAs specific to autophages appeared to be quite similar to that of Intestiphage in those 5 cases.

Assessment of APA levels by neutralization assay.

Neutralizing APA activity in serum was detected in all patients, although the magnitude of the response varied widely depending on the patient and day of sample collection (Figure 1a). The neutralization constant K ranged 0.0 – 1.4 at day 0, prior to phage treatment, started to increase by day 7 (K=0.07-1.9) and at day 14 (an average duration of PT) K comprised 0.2 - 2.3. The highest K values were observed in the patient 10 at all sampling points. Generally, low to moderate neutralization activity ($K \leq 3$) demonstrated by the study patients, is consistent with expectations for short course of local-oral phage therapy using relatively low phage concentrations ($1X10^5$ – $1X10^7$ pfu/

ml). Similar data - low phage neutralization values during early period of PT were shown in the study of Łusiak-Szelachowska [30], namely K = 0.00–0.52 in the patients' sera prior to the PT and relatively increased, but still low K = 0.29–0.67 after 2–2.5 weeks of PT. In our study, for most patients, neutralization activity was markedly higher in serum than in urine or even more than in saliva (Figures 1b, c). Several individuals (P4, P5, P6, P11) displayed zero phage neutralization activity in saliva and also partly in urine, despite measurable responses in their sera. Interestingly, compared to serum, a relatively expressed mucosal reaction - the increased neutralization K was registered at day 14 in saliva and urine of the P7 – the only patient who didn't respond positively to the phage treatment undertaken. Overall, no consistent correlation was observed between neutralization activity across the three biological fluids within individual patients. These findings are in line with usual predominance of systemic antibody elevation while local responses in urine and saliva develop more modestly.

The neutralization assay as well as ELISA (see below) was also performed on samples from six healthy volunteers using the same protocols. Notably, none of the healthy volunteers' samples exhibited measurable neutralization activity against the mixture of the four phages derived from Intestiphage. This may indicate absence of natural neutralizing antibodies in these individuals who have never been treated with phages. At the same time this confirms the characteristics of the neutralization assay which generally detects only specific neutralizing antibodies elicited by recent or earlier sufficiently strong antigenic exposure.

Assessment of APA levels by ELISA.

ELISA results provided additional insight into humoral responses against phages. A total of 117 samples (serum, urine, saliva) from 11 patients and 6 healthy controls were analyzed. ELISA revealed APA activity almost in all biological fluids, with the highest absorbance values recorded in serum (Figures 2a, b, c). Although the optical absorbance was measured at higher dilutions as well, a 1:50 dilution was chosen for APA quantitative detection to maintain consistency across patients and fluids. Maximum absorbance in serum reached 2.5 absorbance units, whereas urine and saliva showed lower peaks, reaching about 1.8 units. These results are in agreement with the concept that systemic antibody responses, particularly to therapeutic phage preparations, is much stronger compared to antibody presence in local biological fluids and mucosal surfaces. Significant intra patient fluctuations were observed during PT course: several patients showed gradual increases over the three sampling points, while others exhibited minimal or delayed responses. These variations likely reflect individual differences in patients' immune status, prior or concurrent treatments, and the extent of bacterial infections.

Interestingly, the serum, urine, and saliva samples from the group of healthy individuals also demonstrated APA absorbance values by ELISA (Figure 3) - lower but still comparable to baseline (day 0) sera from EPTC patients (Figure 2a). However, none of these biological samples, even urine, showed measurable neutralization activity against the same mixture of 4 phages used in the testing in the study cohort. To explain such divergence between the results of the two assays we can assume that natural antibodies, likely arising from exposure to commensal or environmental phages, may bind phage antigens weakly without exerting functional neutralization. These findings are consistent with the understanding that healthy individuals could be naturally exposed to phages as antigens and naturally produce phage-specific antibodies, even if they never received therapeutic phages before [25].

Comparison of average APA levels across the patient cohort and healthy individuals.

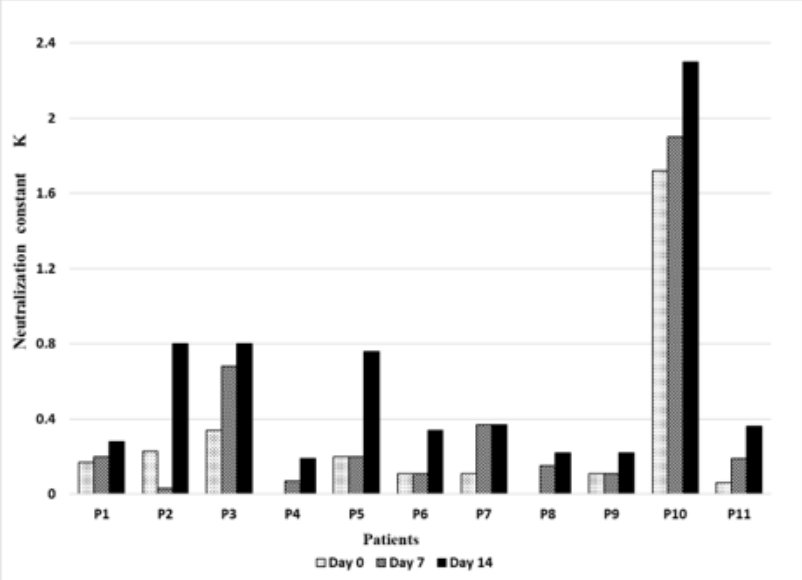
Comparison of average APA levels among all patients measured by neutralization assay and ELISA indicated a pattern of increase after the exposure with phage in all fluids tested (Figures 4a, 4b). At day 7, a statistically significant increase was observed only in ELISA of the serum and urine but not in the saliva. No significant increase was seen by the neutralization assay on day 7. Antibody levels continued to increase with the highest averages on day 14 for all samples and the changes were shown to be significant compared to initial antibody levels observed at day 0. In both assays, especially in neutralization, high interpatient variability was demonstrated, although the phage neutralization results tended to show higher average

Table 1. *Grouping of study patients into categories according to the treatment outcomes*.*

Category A	Category B	Category C	Category D-E
Patient #5 (33 years old, male) Bacterial prostatitis; chronic UTI; combined treatment with commercial phages and antibiotic.	Patient #3 (36 years old, female) Chronic UTI; treatment with the *E. faecalis* autophage and commercial phages.	Patient #1 (85 years old, female) Chronic vaginitis and cystitis with polymicrobial flora; treatment with combination of commercial phages.	Patient #7 (43 years old, female) Chronic Pyelonephritis; treatment with the autophage of *K. pneumoniae* and commercial phages.
Patient #6 (51 years old, male) Chronic UTI; treatment with the *E. faecalis* autophage and Intestiphage, intravesical installations with Intestiphage.	Patient #9 (28 years old, male) Chronic UTI; polymicrobial culture; combined treatment with combination of commercial phages.	Patient #2 (25 years old, male) Chronic prostatitis; treatment with the *E. faecalis* autophage and commercial phages.	
Patient #11 (68 years old, female) Chronic vaginitis, chronic cystitis; combined treatment with commercial phages.	Patient #10 (29 years old, female) Chronic vaginitis, chronic cystitis; treatment with combination of commercial phages.	Patient #4 (34 years old, male) Bacterial prostatitis; combined treatment with commercial phages.	
		Patient #8 (72 years old, male) Chronic UTI; treatment with commercial phages and the *P.aeruginosa* autophage.	

**Description of categories: A - good clinical response to phage therapy with eradication of a pathogen; B - good clinical results with significant reduction of a pathogen; C - clinical stabilization with low to moderate reduction in bacterial counts; D -E - poor (transient) response or no response to treatment without reduction in bacterial counts.*

a



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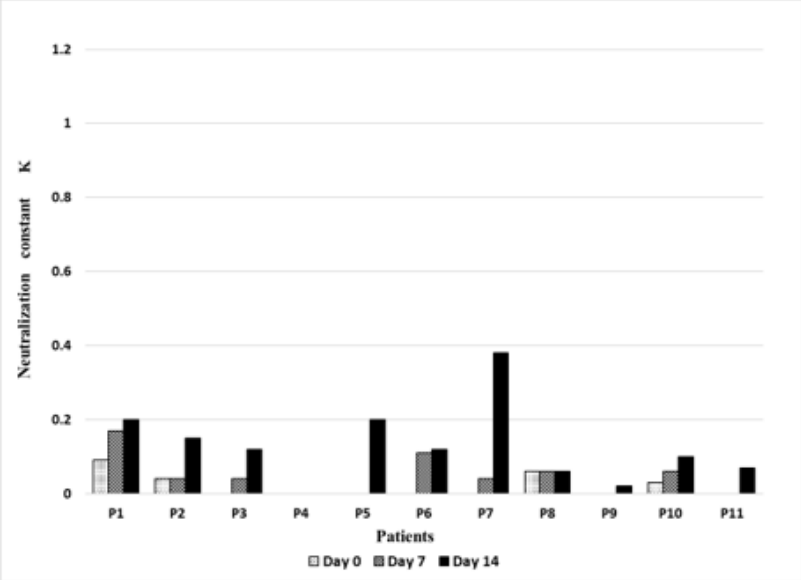

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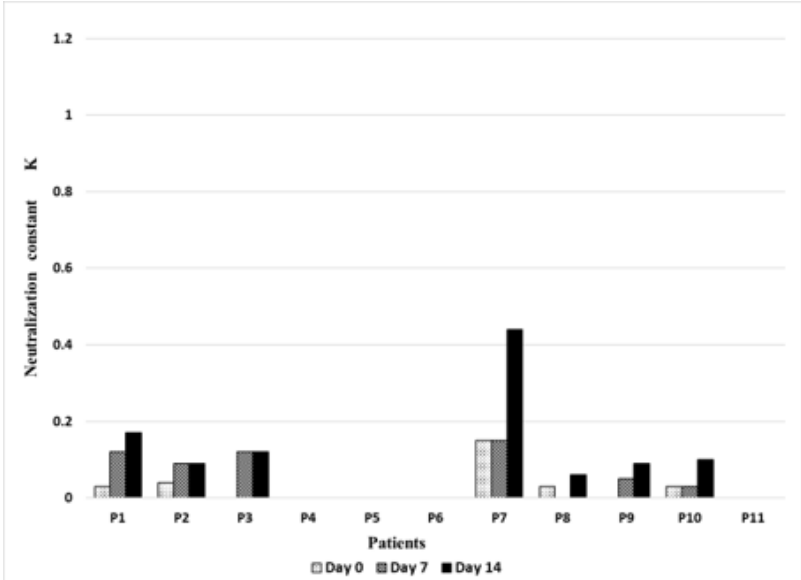
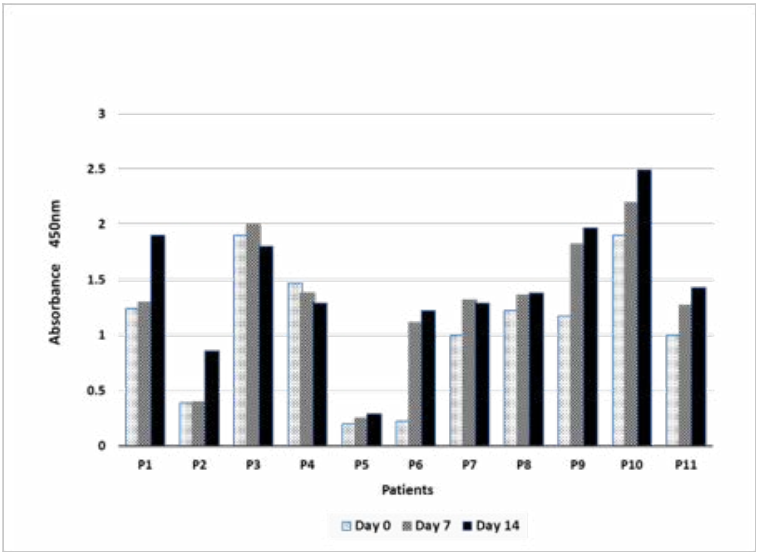


Figure 1. *APAs measured by neutralization assay in biological samples of patients with UTIs during short - term PT presented as neutralization constant (K). a) blood serum; b) urine; c) saliva. Averages of three parallel measurements.*

a



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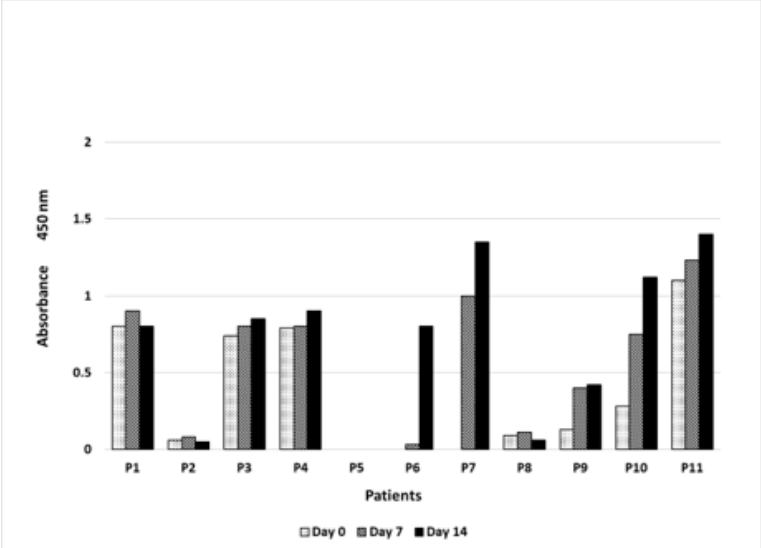

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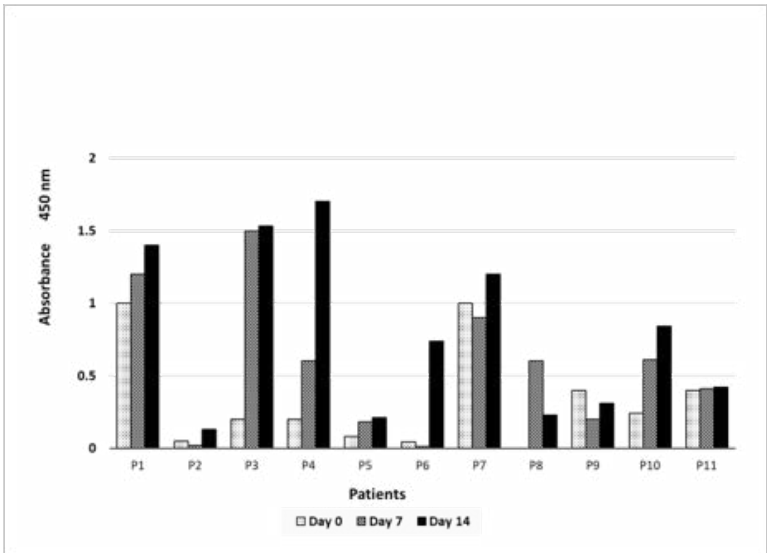


Figure 2. *APAs measured by ELISA in biological samples of patients with UTIs during short - term PT presented as absorbance values at 450 nm. a) blood serum; b) urine; c) saliva; Averages of two parallel measurements.*

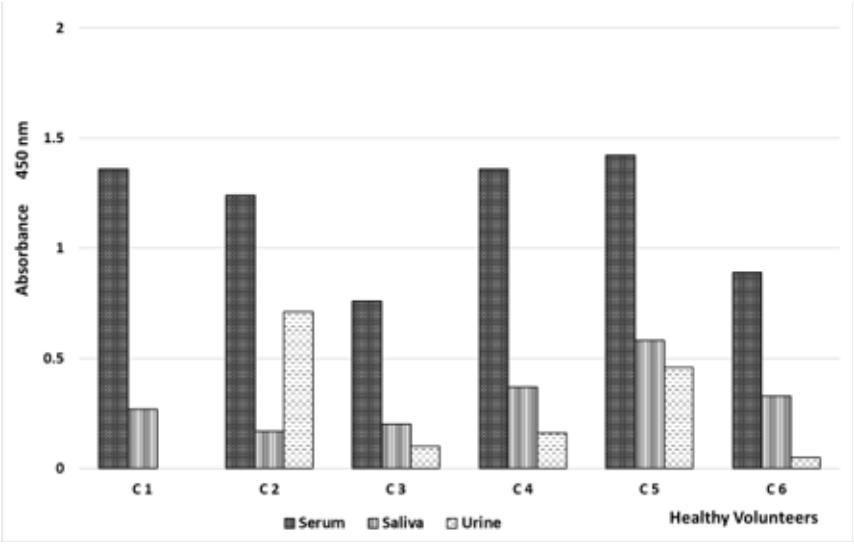
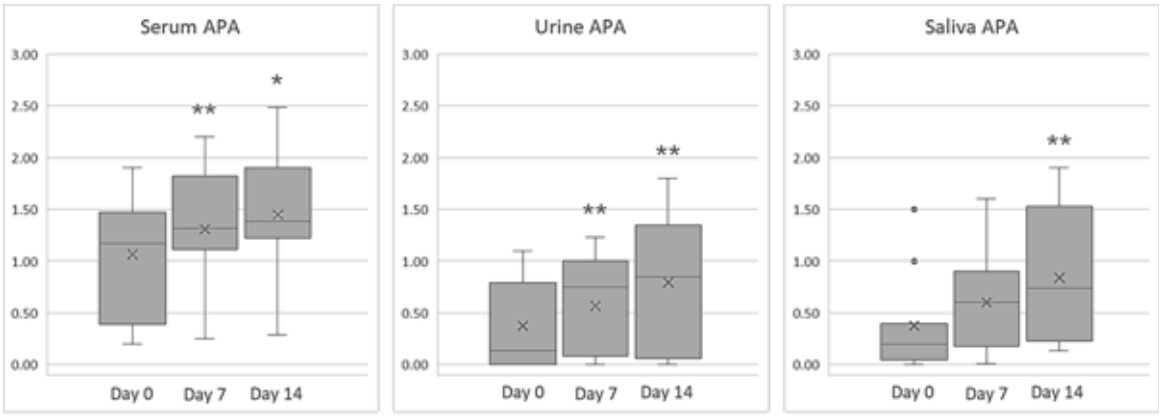


Figure 3. *APAs measured by ELISA in biological samples of patients with UTIs during short - term PT presented as absorbance values at 450 nm a) blood serum; b) saliva; c) urine; Average of two parallel measurements.*

a



b

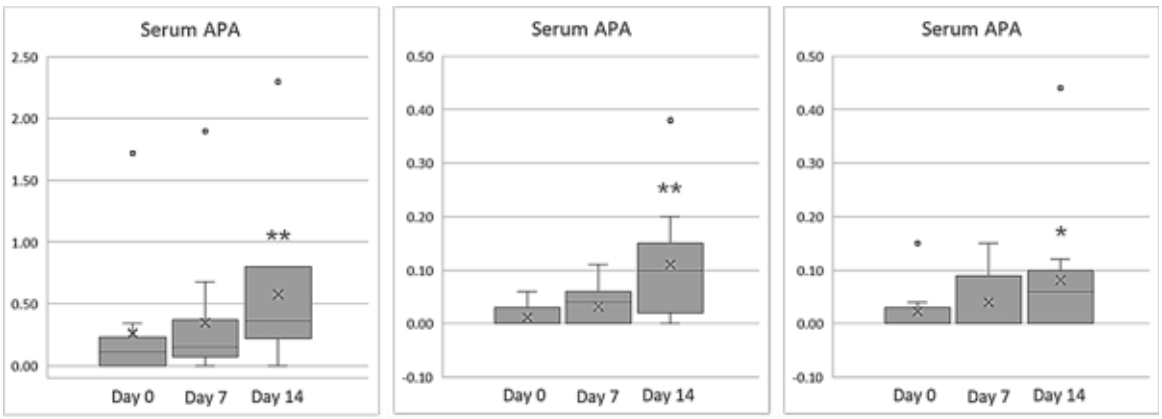


Figure 4. *Box plots of APA levels measured by (a) ELISA and (b) neutralization assays. The box represents the interquartile range. The horizontal line inside the box is the median while the "X" sign is the arithmetic mean. Whiskers indicate the spread except of outlier that is shown as a lone dot outside the whisker. Significances of increase compared to Day 0 was calculated with Wilcoxon matched-pairs signed rank test: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

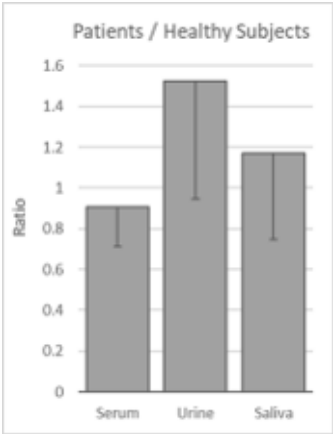


Figure 5. *Ratios of average APA levels between patients before PT (day 0) and healthy subjects measured by ELISA. Whiskers indicate standard errors of means (SEM).*

increase compared to ELISA measurements. The average coefficient of variance (CV) across all samples measured by the ELISA was 47 % for serum, 90 % for urine and 97 % for saliva. In comparison the neutralization showed the following CVs: 154 % for serum, 131 % for urine and 164 % for saliva. The higher variability seen using the neutralization assay compared to the ELISA could indicate patient specific responses in generating neutralizing antibodies that cannot be distinguished by ELISA.

Comparison of average APA levels measured by ELISA revealed no significant differences between the patients before treatment (Day 0) and randomly selected healthy subjects in none of the three sample types (Figure 2). It should be noted that the comparisons between healthy subjects and Day 0 patients should be interpreted cautiously, given potential confounding differences such as age, the chronic infection status, and prior exposure to phage antigens.

The neutralization assay didn't yield any positive outcomes in the fluids of these healthy subjects, indicating the absence of neutralizing antibodies in these samples.

Overall interpretation of treatment efficacy and APA dynamics during short term phage therapy in patients with UTIs.

Major Findings.

The clinical evaluation of these eleven case reports demonstrates the significant potential of phage therapy for managing chronic, antibiotic-resistant UTIs, dominated by vaginitis and cystitis in females, and complicated prostatitis - in males. While the cohort's diverse clinical histories added complexity to the data interpretation, some clear patterns emerged. Despite long-standing infection histories, 10 out of 11 patients (90.9 %) achieved positive clinical outcomes after a relatively short treatment course. Specifically, four patients showed marked improvement alongside the reduction or eradication of pathogens such as *E. faecalis, P. aeruginosa*, and *S. aureus*. Notably, the largest subset achieved clinical stabilization even when laboratory findings were less definitive. Some patients maintained stable remission through continued home treatment with phages. Outcomes were consistent across this small but quite diverse group, indicating that PT can be effective regardless of age (25–86 y) or gender.

Our study demonstrates that APAs develop to varying degrees during short-course therapy, with the strongest responses observed in serum and comparatively low levels in urine and saliva. Despite the variability in the different biological fluids, a general pattern - an increase in APA levels during the two week PT was observed across the patient cohort. Most importantly, the elevated APA levels, including increased ELISA absorbance and higher neutralization constants, did not correlate with poorer clinical outcome. Many patients with high APA responses exhibited significant clinical and microbiological improvement, while some with low APA levels showed only modest therapeutic responses. These observations reinforce the consensus that early humoral immune responses, particularly during short-term treatment, are not inherently detrimental to therapeutic success [21,31,32].

The weak or moderate neutralizing activity among the EPTC patients indicates that short duration of treatment (15 days in average) limited the intensity of the APA production. Since the use of total secondary antibodies prevents isotype -specific interpretation, we can only assume, considering the classical humoral kinetics, that the observed early APA occurrence (starting from 7th day after start of PT) can be driven by initial IgM responses and also possibly by limited early IgG production which generally peaks by ≥3 weeks after antigen exposure [17,22]. When phages are administered locally – orally intensive phage replication occurs at the infection site colonized by target bacteria and likely helps maintain effective phage levels even in the presence of circulating antibodies. The local environment of the urinary tract during infections characterized by high bacterial loads facilitates substantial phage replication and maintains effective phage concentrations even in the presence of antibody-mediated neutralization. To assess the persistence of antibodies to administered phages the patients' samples should be collected and screened for APAs after completion of PT that was impossible to conduct in our study. Lusiak-Szelachowska et al. [21] found that disappearance of APAs may vary from patient to patient and in some cases may take more than a year.

The variability in APA responses observed among patients could be influenced by several factors: the diversity of pathogens, the use of both commercial phage mixtures and custom phages, differences in disease chronicity, prior exposure to phage

therapy, combined treatment with antibiotics or probiotics etc. The inter-individual variations in immune responses certainly can be explained by individual immune profiles, particularly by structural and genetic differences in the human leukocyte antigen (HLA) system [33]. In addition, patients with long standing infections, multiple prior antibiotic treatments, and substantial mucosal inflammation may exhibit altered or dysregulated immune responses, potentially affecting APA kinetics. The observed gradient in APA intensity can be also explained by the administration routes used. Most patients received phages primarily via oral and mucosal routes, which typically induce weaker systemic immunity than parenteral administration - that was used in the majority of animal studies [17,25].

Comparing ELISA and neutralization assays provided additional evidence that these tools provide complementary but distinct information for assessment of the immune response. ELISA, a binding assay, identifies a broad spectrum of antibodies - including natural, cross-reactive, or low-affinity immunoglobulins, whereas neutralization assays detect only the subset capable of impairing phage infectivity. We found that healthy controls and some patients at Day 0 demonstrated measurable ELISA signals but no neutralization activity, indicating that natural antibodies may bind phage components without their functional inhibition. Therefore, we think that the presence of ELISA measured binding antibodies cannot be viewed as a predictor of treatment failure.

Weaknesses and limitations.

Although the aim of this observational research was to assess the PT efficacy in patients with UTIs and provide insight into early immune response during PT and its possible impact on the treatment efficacy, it was limited by its small sample size, heterogeneous study population, consisting of international patients, and restricted follow up. Most notably, the short treatment period and limited availability of post therapy samples prevented the assessment of longer-term APA dynamics. ELISA results obtained with total IgG/M/A secondary antibodies didn't allow to make any definitive statements also regarding early humoral responses. Additionally, use of multi-phage mixtures for PT and, in a number of cases, some adjunctive therapies (immunomodulators, bacterial vaccines etc), also capable to influence the APA production, can be misleading in the interpretations of phage therapy outcomes and related immune responses. The use of semi-purified phage preparations, as antigens, may also complicate the reading of the results in immunological assays, such as ELISA.

Conclusion.

Key Findings and Future Directions.

• A short-term phage therapy of chronic, antibiotic-resistant UTIs is an effective treatment capable of providing clinical stabilization regardless of patient age, gender, or long-standing infection history. The high rate of positive outcomes and stable remissions underscores the potential of PT, primarily personalized phage treatment, as a robust alternative for managing complex urogenital infections when conventional treatments fail. The possible effectiveness of combined application of PT with other adjunctive biological means also has been indicated.

• Early immune response to PT, as measured by APA development, is a natural physiological reaction and does not represent a barrier to successful short term therapeutic phage application in patients with urinary tract infections. Most of the patients showed symptomatic improvement and pathogen reduction despite measurable APA increases during short-term PT with moderate phage doses. These findings support the expanded use of phage therapy for managing chronic and recurrent UTIs.

• Future studies should include longer treatment durations and standardized treatment protocols, homogeneity of the study cohort and extended sampling. The use of patient specific antigen panels matched to individual therapeutic phages and isotype specific ELISA will aid further detailed characterization of humoral immune response, including IgM, IgA, and IgG dynamics across various biological fluids. All this will provide more reliable data for a deeper understanding of the role of host antibody mediated immunity in phage therapy.

Acknowledgments.

The study was conducted within the framework of the project grant EL-UG 2453/1.03.22, jointly funded by the Eliava Foundation- Association for Development of Bacteriophages in Georgia (Tbilisi, Georgia) and the University of Georgia (Tbilisi, Georgia). We are grateful to Dr. Nino Chikadze (University of Georgia) for support in ELISA performance, to Ia Kutateladze (EPTC) for collecting patient's samples and to Tamar Katukia (EADC) for assistance in UTI bacteriology.

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