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Bacteriophage therapy in women with chronic recurrent cystitis caused by multidrug-resistant bacteria: A prospective, observational, comparative study

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Abstract

Objectives: The aim of this study was to evaluate the effects of the combination of bacteriophage therapy with antibiotics and bacteriophage treatment alone on relieving clinical symptoms of chronic recurrent cystitis caused by multidrug-resistant bacteria.

Materials and methods: This clinical trial compared the treatment methods of 217 female patients with chronic recurrent cystitis caused by multidrug-resistant bacteria, who were investigated from June 2020 to May 2023. Patients were allocated into 4 groups: group I: received bacteriophage (Sextaphage) therapy alone; group II: received a combination of bacteriophages (Sextaphage) and furazidin; group III: received a combination of bacteriophage (Sextaphage) and furazidin with cefixime; and group IV: received furazidin and cefixime (without bacteriophage). The primary outcome included changes in the acute cystitis symptom scale and the pain visual analog scale, which were completed on days 7 and 14 following treatment. Secondary outcome measures included bladder diary records of urinary symptoms, median voided volumes, level of bacteriuria, and degree of leukocyturia.

Results: Initially, 217 female patients were presented during baseline visits. Those who did not meet the criteria inclusions were excluded, and 178 female patients were included in the final analysis. Statistically significant improvements from baseline in acute cystitis symptom scale scores for differential, typical symptoms, and quality of life domains were observed after 14 days of treatment in groups II, III, and IV. The pain level measured on the 14th day with the visual analog scale significantly decreased in groups II, III, and IV compared with group I. The patients of group I had a reduction of mean level bacteriuria of *Escherichia coli* from 10^6 to 10^2 CFU/mL at 14 days of therapy. Significant improvement of voided volume from baseline was observed in groups II, III, and IV. Episodes of urinary frequency, both daytime and night-time, reduced significantly from baseline in all 4 groups only at 14 days of treatment.

Conclusions: Bacteriophage cocktail alone or with antibiotics may improve clinical symptoms in women with chronic recurrent cystitis caused by multidrug-resistant bacterial pathogens. In addition to improving clinical symptoms, the therapy with a phage cocktail may restore antibiotic sensitivity and increase the efficacy of antimicrobial agents.

Keywords: Bacteriophages; Antibiotic resistance; Urinary tract infection; Chronic recurrent cystitis

1. Introduction

Urinary tract infection (UTI) caused by antibiotic-resistant microorganisms is a major global problem for patients and their treating urologists, general practitioners, or infection disease specialists.[1,2] Urinary tract infection is extremely common, with 45%–60% of women having experienced a single episode during their lifetime, and with 20%–40% having had a recurrence of UTI within 6–12 months. Long-term recurrence of UTI is also common in up to 50% of those who have experienced an earlier UTI.[3,4] Antimicrobial resistance patterns differ depending on the type and level of antibiotics consumed. In Pakistan, the resistance of ceftriaxone and ciprofloxacin for *Escherichia coli* exceeded 70% in patients with UTI,[5] whereas in the United States, Frisbie et al.[6] have reported that females aged 19–50 years had high rates of resistance to ampicillin (38%) and trimethoprim/sulfamethoxazole (19%). In Israel, Peretz et al.[7] have retrospectively demonstrated that urine cultures with extended-spectrum beta-lactamases-producing bacteria had a higher rate of resistance to fosfomycin, reaching 30.5%. Apart from antibiotics, bacteriophages are a current alternative approach in the potential against antibiotic resistance in urology. Bacteriophages are obligate, self-replicating, intracellular viruses that were discovered by the French-Canadian scientist Felix d'Herelle in 1917. They bind to specific receptors on the surface of bacterial cells, destroying them. Bacterial cells evolve increased phage resistance, but sensitivity to antibiotics increases.[8] Several

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studies about phage therapy have demonstrated benefits either alone or in combination with antibiotic treatment.[9–12] This study evaluates the effects of bacteriophage therapy, both alone and in combination with antibiotics, upon clinical symptoms and urine microscopy findings of chronic recurrent cystitis caused by multidrug-resistant bacteria (MDRB).

2. Materials and methods

2.1. Patient population and study design

This clinical trial included 178 female patients with chronic recurrent cystitis who were investigated from June 2020 to May 2023. The flowchart of the study is shown in Figure 1. The study conformed to the principles of the 1964 Declaration of Helsinki and was approved by independent institutional review boards of the participating centers (IRB approval number: 2950-1990). All patients gave written and informed consent.

2.2. Inclusion criteria

The inclusion criteria are as follows:

1. Age 18 to 75 years;
2. Absence of abnormalities of the urinary tract;
3. Presence in the urine culture of multidrug-resistant bacterial monoinfection, which is sensitive to bacteriophage, furazidin, and cefixime; and
4. More than 2 relapses of disease in 6 months or 3 relapses per year.

2.3. Exclusion criteria

The exclusion criteria are as follows:

1. History or presence of sexually transmitted infections;
2. Uncomplicated cystitis;
3. Asymptomatic bacteriuria;
4. History of upper UTIs;
5. Presence of antibiotic-sensitive bacterial pathogens in urine culture; and
6. History of transurethral procedures (endourological operations and urethral catheterizations).

2.4. Data collection, examinations, interventions, and allocation

All women were subjected to urine cultures and antibiotic susceptibility tests, urine sediment microscopy, polymerase chain reaction of urethral smears, ultrasound investigation of urinary bladder and kidneys, and uroflowmetry. A thorough history was taken, including an assessment of previous endourological operations and urethral catheterizations. Pain levels were measured using a visual analog scale (VAS) before the initiation of treatment as well as after 7 and 14 days. A reduction of over 50% of the VAS score was considered a strong benefit, and less than 50% a limited benefit. No change in the VAS score was considered "no benefit," and an increase in the VAS score was considered "symptom worsening." Clinical symptoms were evaluated using the Russian-language Acute Cystitis Symptom Scale (ACSS) questionnaire[13] before treatment and after 7 and 14 days. The ACSS contains 18 items that are divided into 4 domains: 4 items for differential diagnosis ("differential" domain), 6

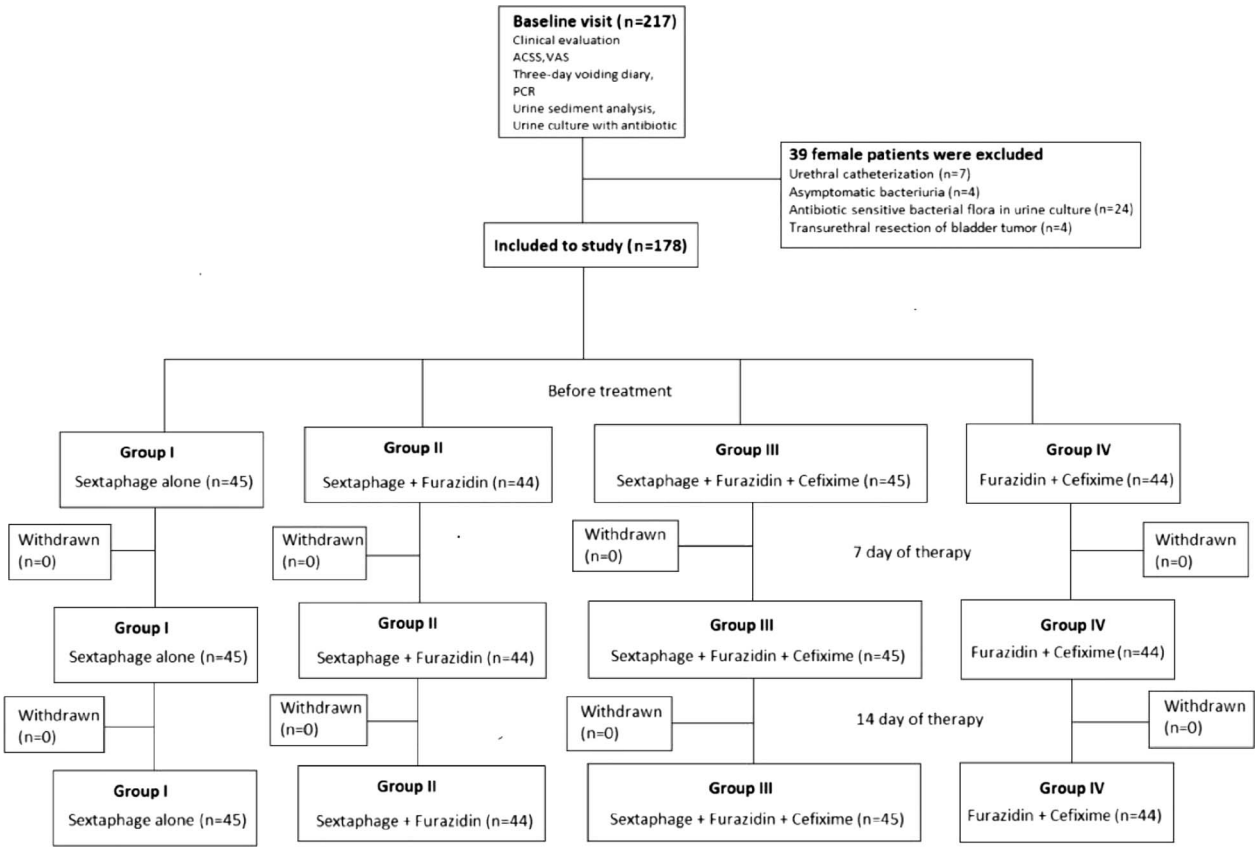

Figure 1. Flowchart of the study. ACSS = Acute Cystitis Symptom Scale; VAS = visual analog scale.

items regarding typical acute cystitis symptoms ("typical" domain), 3 items on quality of life (QoL) domain, and 5 additional questions regarding other relevant conditions ("additional" domain). Patients were also evaluated with a 72-hour bladder diary (urine frequency, nocturia, and voided volumes) before therapy and on days 7 and 14. The microbiological investigation of midstream urine was performed with the following nutrient media: HiCrome selective agar for enterococci; blood agar, prepared based on Müller-Hinton agar with the addition of sheep erythrocytes, and yolk salt agar also before the initiation of the treatment. After 7 and 14 days, only MDRB affected the outcomes. The antibiotic susceptibility was determined using disc diffusion and agar dilution methods in accordance with the Clinical Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing guidelines, which showed that microorganisms were resistant to ampicillin, ciprofloxacin, levofloxacin, amikacin, gentamicin, ceftriaxone, imipenem, meropenem, amoxiclav, co-trimoxazole (sulfamethoxazole-trimethoprim), erythromycin, and clindamycin. The cases of chronic recurrent cystitis caused by bacterial pathogens having antibiotic susceptibility were excluded. All identified female patients with chronic recurrent cystitis caused by MDRB were allocated into 4 groups, with every bacterial species being distributed in each group: group I: received bacteriophage (Sextaphage) therapy alone; group II: combination of bacteriophages (Sextaphage) and furazidin; group III: combination bacteriophage (Sextaphage) and furazidin with cefixime; and group IV received furazidin and cefixime (without bacteriophage). There was no placebo control group. Following patient exclusion, a sequence of random numbers was generated by computer and then assigned to each investigated group. For the random number generator, we used Python program. Sextaphage is a pharmaceutical phage composition made by Joint-Stock Company, Scientific and Production Association, Microgen, the 2nd Volkonsky lane, Moscow, Russian Federation.

This bacteriophage cocktail includes filtrate of phagolysates of 6 bacterial pathogens: *Staphylococcus*, *Streptococcus*, *Proteus* (*P. vulgaris, P. mirabilis*), *Pseudomonas aeruginosa*, enteropathogenic *E. coli*, and *Klebsiella pneumoniae*. The treatment included both monotherapy with bacteriophage cocktail (Sextaphage) (30 mL, orally, 6 times a day) and its combination with cefixime (400 mg once a day) alone or together with furazidin (100 mg 3 times a day).

2.5. Outcomes

The primary outcomes included the change of pain levels measured using the VAS and differential, typical, and QoL domains of the ACSS questionnaire. Secondary outcomes included changes in mean levels of bacteriuria, daily urinary frequency/nocturia, median voided volumes, and levels of leukocyturia in urinary sediments.

2.6. Statistical analysis

A chi-squared test was used to compare the association between categorical variables. The continuous variables were compared using the unpaired Student *t* test. The Kruskal-Wallis *H* test and the 1-way test analysis of variance (ANOVA) were used to compare changes in analyzed parameters among the 3 investigated groups. To determine the necessary sample size, a power calculation was conducted using NQuery 3.0 with a 2-sided significance level of 5% (alpha = 0.05) and power of 90% (beta = 0.1) based on a 2-group *t* test of equal mean values. Based on the primary outcome, the sample size was powered by the ACSS questionnaire and VAS scores. At 90% power and a 5% 2-sided significance level, we estimated a sample size of 44 individuals in each group. Taking account of the 20% dropout rate, we required 45 participants in each group, giving a total sample size of 180. The treatment effects were also compared with the baseline using the 1-way test ANOVA or the Kruskal-Wallis test following the Tukey post hoc test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using Stata software (version 15).

3. Results

3.1. Demographics and baseline characteristics

A total of 217 female patients with chronic recurrent cystitis were recruited for the study from June 2020 to December 2022. During the enrollment period, 39 women were excluded from the study for various reasons, including urethral catheterization ($n = 7$),

Table 1

Baseline clinical and demographic characteristics.

Parameter	Group I (Sextaphage alone)	Group II (Sextaphage + furazidin)	Group III (Sextaphage + furazidin + cefixime)	Group IV (Furazidin + cefixime)	p[b]
Number of patients, n (%)	45 (25.3%)	44 (24.7%)	45 (25.3%)	44 (24.7%)	
Age, yr[a]	38 ± 15	36 ± 17	37 ± 16	36 ± 15	NS
VAS pain score	10	9	10	10	NS
Domains of ACSS questionnaire					
Typical domain[a]	15.5 ± 2.5	16 ± 1.9	15.7 ± 2.4	15.9 ± 1.8	NS
Differential domain[a]	9.5 ± 2.1	9.1 ± 2.9	9.2 ± 2.3	9.3 ± 2.3	NS
Quality of life[a]	8.2 ± 0.9	7.9 ± 1.1	7.6 ± 1.4	7.8 ± 1.2	NS
Amount of WBC in urine[a]	55 ± 24	51 ± 29	52 ± 31	53 ± 28	NS
Voided volume of urine (mL)[a]	21 ± 7.3	24 ± 6.8	22 ± 6.2	23 ± 6.3	NS
Urinary frequency					
Daytime frequency[a]	15 ± 4	14 ± 5	16 ± 5	15 ± 3	NS
Night-time frequency[a]	9 ± 6	9 ± 5	10 ± 4	9 ± 4	NS

[a]Values are given as mean ± standard deviation.

[b]NS: differences were statistically not significant ($p < 0.05$).

p value using the Kruskal-Wallis *H* test.

ACSS = Acute Cystitis Symptom Scale; VAS = visual analog scale; WBC = white blood cells.

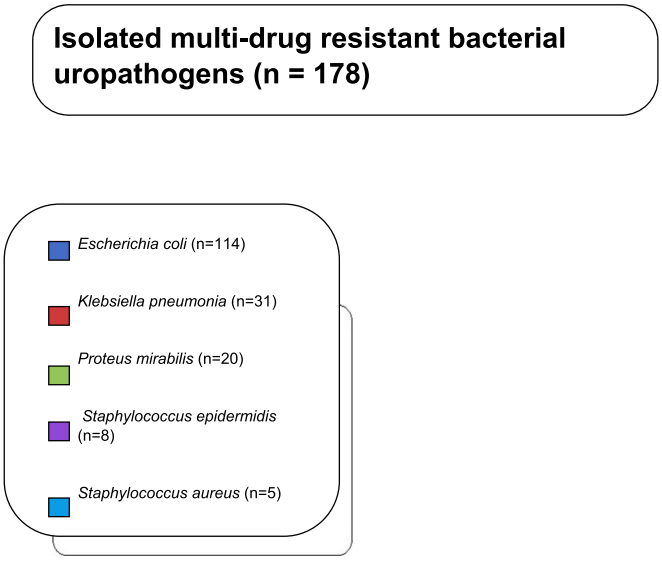

Figure 2. Isolated multidrug-resistant bacterial pathogens in studied population.

asymptomatic bacteriuria (n = 4), antibiotic-sensitive bacterial flora in urine culture (n = 24), and transurethral resection of bladder tumor (n = 4). A total of 178 female patients were included in the final analysis. The duration of treatment was 14 days. Baseline demographic and clinical characteristics are presented in Table 1. Before treatment, all patients were confirmed to have grown multidrug-resistant bacterial flora from a urine culture with an antibiotic sensitivity test. All isolated microorganisms were resistant to many commonly used antibiotics in urology: ampicillin, ciprofloxacin, levofloxacin, amikacin, gentamicin, ceftriaxone, imipenem, meropenem, amoxiclav, co-trimoxazole (sulfamethoxazole-trimethoprim), erythromycin, and clindamycin. The isolated multidrug-resistant bacterial pathogens before therapy are shown in Figure 2. The resistance rates to each antibiotic for all isolated microorganisms are shown in Table 2. All 4 groups had similarly high scores on ACSS and VAS questionnaires. There was no statistically significant difference among the 4 groups in terms of baseline demographic and clinical parameters.

3.2. Primary outcomes

ACSS questionnaire and VAS scale Statistically significant improvements were observed in the ACSS score for the differential, typical symptoms, and QoL domains after 14 days of treatment in groups II, III, and IV compared with group I. Pain levels measured with the VAS significantly decreased in groups II, III, and IV (1, 0, 1), compared with group I (4) on the 14th day (Table 3). The post hoc analysis demonstrated statistically significant differences between groups I and II, III, and IV in the improvement of symptoms during treatment. The comparison of ACSS scores between groups III and IV had statistically significant differences as well. However, there were no statistically significant differences between group II and groups III and IV (Table 3).

3.3. Secondary outcomes

The mean level of bacteriuria There were no statistically significant differences in baseline mean level bacteriuria among the 4 groups. Group I had a decrease in the mean *E. coli* bacteriuria levels from 10^6 to 10^4 CFU/mL at 7 days of treatment and from 10^4 to 10^2 CFU/mL after 14 days of therapy. The changes in bacterial count in 1 mL of urine for each isolated microorganism during treatment are depicted in Figure 3.

Patients in group I showed restored sensitivity to ciprofloxacin and ceftriaxone but remained resistant to ampicillin, levofloxacin, amikacin, gentamicin, imipenem, meropenem, amoxiclav, co-trimoxazole (sulfamethoxazole-trimethoprim), erythromycin, and clindamycin at 14 days. The levels of bacteriuria in groups II, III, and IV were significantly decreased at 7 and 14 days compared with the baseline values.

The data of the 3-day voiding diary Significant improvements in voided volume were observed in groups II, III, and IV compared with group I after 7 and 14 days of treatment. In groups II, III, and IV, the daytime urinary frequency decreased from 14 ± 5, 16 ± 5, and 15 ± 3 to 3 ± 2, 3 ± 2, and 3 ± 1 only on day 14 of treatment accordingly. Night-time urinary frequency decreased to 2 ± 1, 1 ± 1,

Table 2

Resistance rate (%).

Antibiotics	*E. coli* (n = 114)	*K. pneumoniae* (n = 31)	*Proteus mirabilis* (n = 20)	*S. epidermidis* (n = 8)	*S. aureus* (n = 5)
Beta-lactams					
Amoxiclav	45.9	81.4	83.5	70.7	58.15
Ampicillin	57	-	-	95	87.9
Ceftriaxone	29.5	23.5	53.8	-	-
Imipenem	19	55	10.4	-	-
Meropenem	10.5	14	8.3	-	-
Cefixime	0	0	0	0	0
Fluoroquinolones					
Ciprofloxacin	60.6	46.3	45.4	-	-
Levofloxacin	10	15.4	19.4	42.5	46.5
Aminoglycosides					
Amikacin	2	14	-	62.5	17.4
Gentamicin	22	24.5	51	35.7	29.3
Other					
Sulfamethoxazole/trimethoprim	31	54	81.6	60	5
Erythromycin	-	-	-	73.1	66.4
Clindamycin	-	-	-	21.9	16.8
Furazidin	0	0	0	0	0

Table 3

The comparison of ACSS questionnaires and VAS pain levels before treatment, at 7 and 14 days.

	Group I (Sextaphage alone)			Group II (Sextaphage + furazidin)			Group III (Sextaphage + furazidin + cefixime)			Group IV (furazidin + cefixime)				Post hoc Tukey test					
	Before	7 days	14 days	Before	7 days	14 days	Before	7 days	14 days	Before	7 days	14 days	*p* (ANOVA)	$P_{1,2}$	$P_{1,3}$	$P_{1,4}$	$P_{2,3}$	$P_{2,4}$	$P_{3,4}$
Domain of ACSS questionnaire[a] (total score)																			
Typical domain[a]	15.5 ± 2.5	11.7 ± 2.1	5.7 ± 2.1	16 ± 1.9	10.7 ± 2.4	2.7 ± 1.5	15.7 ± 2.4	11.1 ± 2.2	2.1 ± 1.4	15.9 ± 1.8	10.8 ± 2.1	2.3 ± 1.6	<0.05	0.02	0.013	0.001	0.78	0.80	0.012
Differential domain[a]	9.5 ± 2.1	5.5 ± 1.6	3.5 ± 1.6	9.1 ± 2.9	5.1 ± 1.8	1.1 ± 0.8	9.2 ± 2.3	5.3 ± 1.5	1.3 ± 0.6	9.3 ± 2.3	5.2 ± 1.4	1.2 ± 0.9	<0.05	0.01	0.03	0.002	0.69	0.45	0.029
Quality of life[a]	8.2 ± 0.9	5.2 ± 1.0	3.2 ± 1.0	7.9 ± 1.1	5.1 ± 0.9	1.2 ± 0.5	7.6 ± 1.4	5.0 ± 0.8	1.4 ± 0.7	7.8 ± 1.2	5.2 ± 0.6	1.4 ± 0.7	<0.05	0.03	0.002	0.02	0.82	0.67	0.034
VAS scale value	10	6	4	9	7	1	10	7	0	10	7	1	<0.05	0.04	0.001	0.01	0.95	0.87	0.038

$P_{1,2}$, $P_{1,3}$, and $P_{1,4}$ denoted comparisons of group I with group II, group III, and group IV, respectively. $P_{2,3}$ and $P_{2,4}$ denoted comparisons of group II with group III and group IV, respectively. $P_{3,4}$ denoted a comparison between group III and group IV.
[a]Data are presented as mean ± standard deviation.
p value by ANOVA + Tukey post hoc test ($p < 0.05$ is considered statistically significant).
ACSS = Acute Cystitis Symptom Scale; ANOVA = 1-way analysis of variance; QoL = quality of life; VAS = visual analog scale.

and 2 ± 1 in groups II, III, and IV accordingly (Table 4). The post hoc analysis demonstrated that there were no statistically significant differences among the groups in the improvement of voided volume and urinary frequency during treatment (Table 4).

The level of leukocyturia In all 4 groups, the decline of the level of leukocyturia was not statistically significant at 7-day results but statistically significant on the 14th day of treatment. It decreased from 55 ± 24 to 10 ± 4 in group I, from 51 ± 29 to 9 ± 3 in group II, in group III, the parameter became equal to 8 ± 4, and in group IV, it became 9 ± 5 (Table 4).

4. Discussion

In recent years, following widespread antibiotic use, there has been an emergence of multiantibiotic-resistant strains of bacterial uropathogens.[14,15] The search and development of alternative approaches for treating UTIs caused by resistant multidrug-resistant microorganisms are crucial.[16] Bacteriophage therapy is considered a potentially effective method for treating bacterial infections caused by multidrug-resistant pathogens.[17]

According to our data, the combination of a bacteriophage cocktail (Sextaphage) with antibiotics (furazidin + cefixime or furazidin alone) had a more significant effect on the clinical symptoms of chronic recurrent cystitis than bacteriophage monotherapy. In the human urine model, Grygorcewicz et al.[18] have demonstrated similar effects of the combination of a bacteriophage cocktail and some of the antibiotics commonly used for the treatment of UTI (sulfamethoxazole/trimethoprim, ciprofloxacin, levofloxacin, imipenem, and meropenem) in the eradication of biofilm biomass of *Acinetobacter baumannii*.

The women who received combination therapy experienced a statistically significant decrease in pain syndrome measured with the VAS, urinary frequency, level bacteriuria, and amount of leukocytes in urine after 14 days of treatment. Additionally, they showed a statistically significant improvement in scores of all domains of the ACSS questionnaire (differential, typical symptoms, and QoL domain) and an increased volume of voids after 14 days of therapy.

Bacteriophage therapy has been described in several clinical trials, demonstrating promise in treating UTIs caused by antibiotic-resistant uropathogens. In a randomized, placebo-controlled, double-blind study, Leitner et al.[19] have shown that intravesical bacteriophage therapy with Pyophage was not less effective than standard antibiotic treatment but was also not more effective than placebo. In a case report of a 56-year-old man with recurrent UTI, Terwilliger et al.[20] have demonstrated that the use of a bacteriophage cocktail along with ertapenem may lead to complete bacterial eradication and prevention of phage resistance. In another case, a 63-year-old woman with recurrent UTI caused by multidrug-resistant *Klebsiella pneumoniae* was successfully treated by Bao et al.[21] The combination of sulfamethoxazole-trimethoprim and a phage cocktail effectively treated the disease despite initial resistance to the antibiotic.[21]

Bacteriophages and antibacterial agents are thought to be able to reinforce each other, thereby amplifying their independent effects.[22–24] Our findings support this idea as we demonstrated that a combination bacteriophage cocktail with 1 or 2 antibiotics may enhance therapeutic efficacy. Bacteriophage monotherapy may also improve clinical symptoms of chronic recurrent cystitis and decrease the level of bacteriuria. Unfortunately, at this stage, it is not clear what the long-term impact on the recurrence of UTIs would be.

Figure 3. Boxplots for *Staphylococcus epidermidis* and *Staphylococcus aureus* were not constructed due to small sample of patients.

Phages may help restore bacterial susceptibility to antibiotics. One mechanism by which this occurs is through the alteration of the efflux pump mechanism, achieved by the binding of lytic bacteriophages to the receptor-binding sites on the outer membrane of MDRB.[8] Valério et al.[25] have reported that the combination of phage and ciprofloxacin at sublethal concentrations significantly decreased the levels of *E. coli* bacteriuria compared with phage or antibiotic alone. Pereira et al.[26] has reported that the nosocomial bacterium *Enterobacter cloacae* remained viable but with lower bacterial counts than those in the control group without treatment after 5 days of incubation with a bacteriophage cocktail.

While we observed some promising results, our study has limitations. There is no placebo group. Bacteriophage research is still relatively new, so there is no standardization for formulation or duration of treatment. Moreover, rapid diagnostic tests for phage-antibiotic interactions need to be readily available. Although some positive results were observed in this study, they do not explain the specific mechanisms of antibiotic resensitization due to phage interaction during bacteriophage treatment.

5. Conclusions

A bacteriophage cocktail, either alone or in combination with antibiotics, may improve clinical symptoms in women with chronic recurrent cystitis caused by multidrug-resistant bacterial pathogens. In addition to symptom improvement, therapy with a phage cocktail may resensitize microbes to antibiotics. Based on our results, we believe that starting treatment with bacteriophages and then using antibiotics to which there is no resistance could be an effective treatment regimen. There is a need for larger, placebo-controlled clinical studies to explore this area.

Acknowledgments

None.

Statement of ethics

This study has been approved by the independent institutional review boards of the participating centers (IRB approval number 2950-1990). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients. Informed consent was obtained from all individual participants included in the study.

Conflict of interest statement

All authors declare that they have no conflicts of interest.

Funding source

None.

Table 4

The comparison of level leukocyturia, voided volume of urine, and urinary frequency from baseline at 7 days (A) and 14 days (B) of treatment in 4 groups.

Variables	Group I (Sextaphage alone)			Group II (Sextaphage + furazidin)			Group III (Sextaphage + furazidin + cefixime)			Group IV (Furazidin + cefixime)			*p* (Kruskal-Wallis *H* test)	Post hoc Tukey test				
	Before	7 days	14 days	Before	7 days	14 days	Before	7 days	14 days	Before	7 days	14 days		$P_{1,2}$	$P_{1,3}$	$P_{1,4}$	$P_{2,3}$	$P_{2,4}$	$P_{3,4}$
Amount of WBC in urine[a]	55 ± 24	21 ± 7	10 ± 4	51 ± 29	20 ± 5	9 ± 3	52 ± 31	22 ± 6	8 ± 4	53 ± 28	21 ± 3	9 ± 5	<0.05	0.062	0.073	0.08	0.182	0.093	0.178
Voided volume of urine, mL[a]	504 ± 73	1344 ± 63	920 ± 42.9	552 ± 68	1100 ± 101.5	750 ± 71.4	572 ± 62	1120 ± 116	616 ± 75.6	552 ± 44.1	1100 ± 127.8	750 ± 48.6	<0.05	0.059	0.083	0.172	0.052	0.086	0.102
Urinary frequency																			
Daytime frequency[a]	15 ± 4	9 ± 3	5 ± 1	14 ± 5	6 ± 4	3 ± 2	16 ± 5	6 ± 3	3 ± 2	15 ± 3	6 ± 5	3 ± 1	<0.05	0.042	0.031	0.023	0.033	0.014	0.019
Night-time frequency[a]	9 ± 6	7 ± 2	3 ± 2	9 ± 5	4 ± 1	2 ± 1	10 ± 4	4 ± 2	1 ± 1	9 ± 4	4 ± 1	2 ± 1	<0.05	0.038	0.024	0.031	0.044	0.011	0.020

$P_{1,2}$, $P_{1,3}$, and $P_{1,4}$ denoted comparisons of group I with group II, group III, and group IV, respectively. $P_{2,3}$ and $P_{2,4}$ denoted comparisons of group II with group III and group IV, respectively. $P_{3,4}$ denoted a comparison between group III and group IV.
[a]Data are presented as mean ± standard deviation.
p value using Kruskal-Wallis *H* test + Tukey post hoc test ($p < 0.05$ is considered statistically significant).
WBC = white blood cells.

Author contributions

DK: Research design, writing, data analysis, project development;
NI: Editing, writing;
GB: Editing, manuscript review;
VC: Manuscript review, data analysis;
FG: Manuscript review;
SAG: Data collection;
AEM: Manuscript review.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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