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Evaluation and assessment of the effects of various antibiotics and phages on staphylococcus aureus bacteria

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Abstract: Pyogenic cocci are among the most significant pathogens responsible for both hospital-acquired and community-acquired infections, leading to considerable morbidity and mortality worldwide. Over the past few decades, since the advent of antibiotics, the emergence and spread of methicillin-resistant Staphylococcus aureus (MRSA) have become a serious healthcare challenge. In this study, patients with Staphylococcal infections were observed in two major hospitals located in Tashkent city. Monitoring revealed a sharp increase in infection rates over the last three years, particularly in 2021-2023, with 3,695 infections recorded at the Tashkent Medical Academy and 14,632 cases at the Republican Scientific Center for Emergency Medical Care during the same period. Considering this situation, the effects of various antibiotics and bacteriophages as alternative treatments for Staphylococcus infections were studied. Results showed significant effectiveness with Cefoperazone + Sulbactam (2.8 cm), Fosfosin (2.7 cm), Cefepime (2.7 cm), Amikacin (2.6 cm), Levofloxacin (2.7 cm), Doxycycline (2.6 cm each), and Levomycetin (2.7 cm). The bacteriophage demonstrated an efficacy of 1.5 cm within 12 hours.

Keywords: Staphylococcus, bacteriophages, enterocolitis, pathogenic, lysis, pyogenic, embryo, sterile, colony, virulent.

Introduction: Among epidemiologists, microbiologists, and clinicians, there is a widely accepted notion that virtually no non-pathogenic Staphylococcus species exist [2]. However, there have been cases where Staphylococcus isolates from blood, tissues, and organs exhibit no pathogenic traits [4]. Interestingly, when these bacteria are removed from the body, signs of illness often disappear. This phenomenon should be considered in the laboratory diagnosis of staphylococcal infections [5]. Unfortunately, in our country, routine bacteriological laboratories can only identify Staphylococcus aureus, Staphylococcus epidermidis, and Staphylococcus saprophyticus. Staphylococci primarily affect the skin, skin appendages, and subcutaneous tissues [6]. They are known to cause conditions such as furuncles, carbuncles, felons, paronychia, abscesses, phlegmons, mastitis, lymphadenitis, and wound suppuration in operating rooms [9]. In children, staphylococci are observed as causative agents of staphylodermia, epidemic pustules, and impetigo. They can also cause diseases such as pleuritis, bronchitis, pneumonia, and peritonitis [7]. Staphylococci may lead to tonsillitis, sinusitis, otitis, conjunctivitis, and, in rare cases, infections such as meningitis, brain abscess, myocarditis, endocarditis, arthritis, and infections in vascular prostheses. Dangerous cases of foodborne poisoning, enterocolitis, cholecystitis, cystitis, pyelitis, and pyelonephritis have also been linked to staphylococcal infections [11]. These microorganisms can enter the bloodstream and bone marrow, resulting in sepsis, osteomyelitis, and toxic shock syndrome. The etiology of staphylococcal infections is generally not considered to be acute infectious [10]. The growing antibiotic resistance of microorganisms, particularly staphylococci, has become increasingly significant in treating these diseases [9].

Bacteriophages, or simply "phages," are viruses capable of destroying bacteria, with the following advantages:

1. Target specificity: Phages target specific bacteria without harming human cells or beneficial microflora, potentially making them safer than antibiotics.

2. Effectiveness against resistance: Bacteria may develop resistance to antibiotics, but phages co-evolve with bacteria, making them effective against resistant strains.

3. Natural eliminators: Phages naturally exist in ecological systems, making them safe and environmentally friendly.

4. Fewer side effects: Unlike antibiotics, phages only affect targeted bacteria, leading to fewer side effects.

5. O Wide research potential: Research on phages is ongoing, and since their capabilities are not yet fully explored, there is potential for developing new treatments [13].

In the search for alternative laboratory diagnostic methods, phage diagnostics stand out as a labor-efficient, rapid method applicable at all laboratory levels. The use of bacteriophages in surgery plays a significant role in treating infected wounds, as it directly influences the infection process. The application of bacteriophages, discovered by Félix d'Hérelle in 1917, opened new horizons in surgical practices. Thousands of cases in France were treated with bacteriophages, demonstrating the extensive experience supporting phage therapy [11]. Based on these scientific findings, it was decided to apply bacteriophages for patients with identified Staphylococcus infections. We know that the number of antibiotics used in combating infections is increasing, along with their adverse effects on the body. Antibiotics tend to reduce immune system indicators, diminishing their effectiveness against infections as bacteria quickly adapt to them [2]. Therefore, the primary objective of this study is to isolate Staphylococcus bacteriophages and environmental samples. The research was conducted in the Purulent Surgical Department at Tashkent Medical Academy, employing the H. G. Huxley method [12].

METHODS

At the beginning of the study, Staphylococcus was cultivated in a nutrient medium. Bacteriological examination of the purulent material was conducted on days 3 and 5 before and after infection, ensuring that the sample was introduced into the nutrient medium within 1-2 hours of collection to prevent the infection from deteriorating. The purulent material was collected using sterile cotton and, after initial microscopy, the grown colonies were transferred to a solid nutrient medium using the Gold method for further quantification. A swab was then immersed in sugar broth. If there was no growth on the solid nutrient medium, the study continued by transferring from the sugar broth to the solid nutrient medium. The following nutrient media were used to isolate aerobic microorganisms: 5% blood agar, egg-yolk-salt agar, and Sabouraud agar. Once growth was observed, the number of colonies was calculated and recalculated to determine the level of colonization, expressed as CFU per swab or CFU per ml. The equipment used is specified. Cultures on CA and JSA were incubated under normal conditions for 18-24 hours at 1-37°C. The progression of the infection was monitored. In blood agar, infection growth was observed within 24 hours, and in JSA, Staphylococcus revealed its morphology within 48 hours.

RESULT

Using these methods, Staphylococcus infection was examined. Based on the analysis of results, Staphylococcus bacteria were identified. The findings were prepared in a table format from analyses of samples obtained from the Purulent Wound Surgery Department of the Tashkent Medical Academy.

Table 1
Infections Identified in Analyses from the Purulent Wound Surgery Department

№	Name of Analysis	Type of Infection	Type of Infection
1	Throat	*Staphylococeus aureus*	*Candida albicans*
2	Urine		+
3	Nasal cavity		+
4	Ear		+
5	Pertussis		+
6	Stool		+
7	Intestinal flora in stool		+
8	Uppae leg wound	+	
9	Gluteal wound	+	
10	Lung abscess	+	
11	Sputum		+
12	Thigh wound	+	
13	Abdominal cavity	+	
14	Index finger wound	+	
15	Vagina		+
16	Breast mastitis	+	
17	Skin		+
18	Pus	+	
19	Big toe	+	
20	Cervical canal		+
21	Tonsils		+
22	Mother's milk	+	
23	Prostatic fluid		+
24	Cerebrospinal fluid	+	
25	Hemoculture	+	

The table presents data on patients from the purulent wound surgery department where Staphylococcus aureus was identified in their analyses. Specifically, Staphylococcus aureus was detected in samples taken from the big toe. Additionally, in women, Staphylococcus infection was found in samples from mastitis nodules that intensified and became purulent during the postpartum period. Due to severe respiratory infections, lung abscesses formed, and analyses from this purulent material also confirmed the presence of Staphylococcus. The site and type of analysis are shown in the table, along with the growth in the nutrient medium (Figure 1).

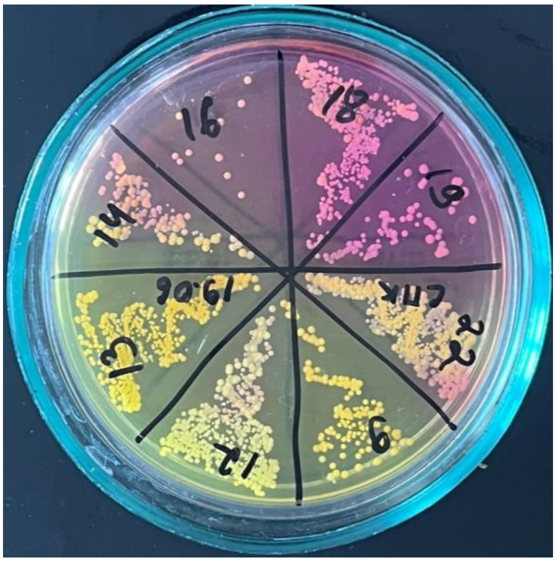

Figure 1. Appearance of Staphylococcus aureus bacteria in Endo nutrient medium.

The numbers indicate the patients' test results.When samples from patients in the Purulent Wound Surgery Department of the Academy were inoculated into the nutrient medium, bacterial growth was observed (Figure 1). These microorganisms were cultured as a lawn, and after growth, various antibiotic diffusion discs were placed on the microorganisms to monitor their activity. The results are shown below in Figure 2.

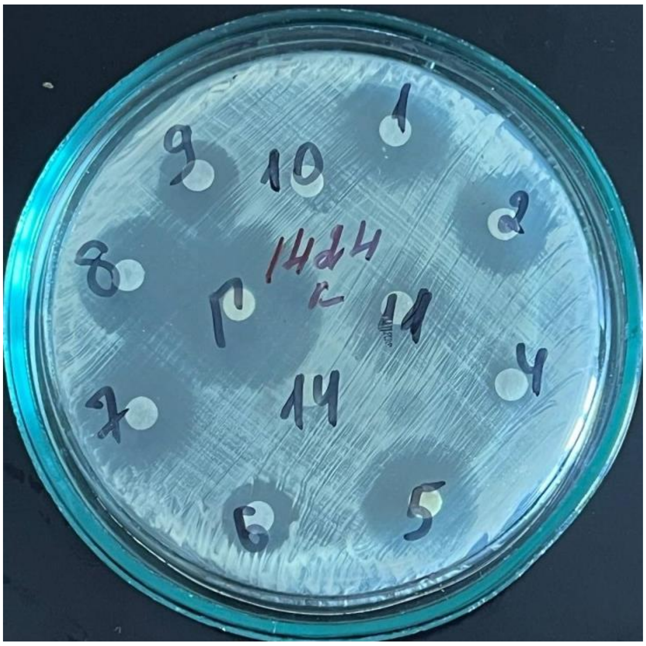

Figure 2. The effect of antibiotics on Staphylococcus infection

In this case, the numbers beneath indicate the antibiotics that had the most effective impact. Cefperazone+sulbactam showed a good effect with a 2.8 cm inhibition zone, Fosfomycin exhibited a 2.6 cm effect. Cefepime also showed a 2.7 cm zone, Amikacin 2.6 cm, Levofloxacin 2.6 cm, Doxycycline 2.6 cm, and Chloramphenicol 2.7 cm showed their efficacy. All of these results are displayed in Figure 2. Antibiotics are working well, showing 50-60% effectiveness.

Currently, leading researchers and scientific centers involved in phage therapy include the Eliava Institute (Georgia), which has been a center for Georgian phage therapy since the 1920s and continues to conduct extensive research on treating various bacterial infections using phages. Texas A&M University (USA) actively conducts research on bacteriophage therapy, and along with other research centers, is exploring the combined use of phages with antibiotics. Yale University (USA), particularly in the engineering field, has research on creating effective phages against bacteria. Biotechnology companies like Phagelux, Adaptive Phage Therapeutics, and Armata Pharmaceuticals are developing alternative treatments to antibiotics through phage therapy in the pharmaceutical industry. Institut Pasteur (France) is also renowned for its research on phages and the development of new phage therapy strategies. These centers and scientists play a leading role in developing

phage therapy as an effective alternative to traditional antibiotics. Several scientific centers are conducting research on combating antibiotic-resistant infections using bacteriophages. For instance, the University of California, San Diego School of Medicine (UCSD) is attempting to use bacteriophages effectively in clinical trials. These studies, conducted over many years for patients with limited treatment options, help to explore the impact of phage therapy on the immune system, determine dosages, and durations. Research shows that bacteriophages are not only effective against antibiotic-resistant bacteria but also exhibit less resistance. Additionally, the World Health Organization (WHO) supports exploring the possibilities of bacteriophage therapy as an alternative to antibiotics and has launched several research programs to gather more scientific evidence in this area. They are specifically studying the effectiveness of using bacteriophages to reduce antibiotic-resistant bacteria in the human body. Also, Zhengzhou University in China is conducting research to expand the use of bacteriophages in combating bacteria like antibiotic-resistant Staphylococcus aureus. These studies propose new methods for treating highly resistant bacteria using bacteriophages and suggest that phage therapy could be an important tool in combating infections resistant to antibiotics in the future, with ongoing scientific research in this field. The properties of bacteriophages and their significance in the epidemiology of infectious diseases are important areas of research. The interaction between bacteriophages and bacteria demonstrates an effective impact in treating diseases. The first studies in this area were conducted by D. Herelle Felix, who studied cultures of bacteria grown with bacteriophages on solid nutrient media (e.g., agar-agar)[11]. During these studies, Felix discovered that bacteria dissolve under the influence of bacteriophages, forming sterile "spots" that result from the dissolution of bacterial colonies under the effect of bacteriophages. Once bacteriophages enter a bacterium, they begin to produce a special enzyme—lysin—which breaks down bacterial proteins and increases internal pressure, causing the bacterium to burst and release a large number of new bacteriophages. After a bacterium bursts, between 12 to 87 new bacteriophages can be produced. Research has shown that the reproduction rate of bacteriophages depends on their virulence. Highly virulent bacteriophages can double the number of new progeny within 10-20 minutes, while less virulent phages take 40-60 minutes. This depends on the type and properties of the phages. Our research tested the effectiveness of phage therapy against infections, comparable to antibiotics. After detecting the infection, it was inoculated in a Petri dish using the lawn method, and Mediaphag Staphylococcus liquid bacteriophage was applied. Within 12 hours, our bacteriophage showed an efficacy of 1.4 cm. This method confirms the effectiveness of phage therapy. When observing bacteriophages under a microscope, swelling and bursting of bacterial cells are observed 30-35 minutes after being added to the bacterial culture. After the cells disintegrate, the liquid contains fine granules and amorphous masses instead of bacteria. Once the bacteria are completely dissolved, the liquid appears completely transparent, and ultramicroscopic bacteriophage embryos are present. Phage therapy plays a significant role in combating diseases such as cholera, typhoid, and dysentery.

Figure 3. The effect of bacteriophage on Staphylococcus aureus.

We tested the effect of bacteriophage on the Staphylococcus infection identified in our dish. The impact of the bacteriophage on the infection was observed within 12 hours, with the bacteriophage inhibition zone reaching up to 1.4 cm. This demonstrates the effectiveness of the bacteriophage, yielding positive results using MediPhag's liquid bacteriophage specific to Staphylococcus aureus.

CONCLUSION

Although antibiotics are used as an aid against infection in the body, their side effects can weaken the immune system and reduce the body's ability to combat infections. Antibiotics provide only a temporary effect without fully eliminating the infection, which may lead to the recurrence of infection. In contrast, bacteriophages target only the infection without harming the body's immune system. Observations show that the Staphylococcus aureus bacteriophage from MediPhag demonstrated high efficacy and yielded more positive results compared to antibiotics. Notably, Cefoperazone + Sulbactam (2.8 cm), Fosfomycin (2.6 cm), Cefepime (2.7 cm), Amikacin (2.6 cm), Levofloxacin (2.7 cm), Doxycycline (2.6 cm each), and Chloramphenicol (2.7 cm) showed effectiveness. The bacteriophage, within 12 hours, displayed its effect with an efficiency of 1.4 cm.

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