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Treatment of *Staphylococcus aureus* Infections in Humans by Phage Therapy as an Alternative to Antibiotics

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ABSTRACT

Due to their potency against bacterial illnesses, the manufacture and use of antibiotics both greatly rose after World War II. However, bacterial resistance also developed and is currently a significant global problem. The high-risk individuals who require the most intensive treatment include those who suffer burns and various other wounds, and also those who have infections of the lungs caused by bacteria that have antibiotic-resistant, such as *P. aeruginosa*, *Acinetobacter* spp. & *Staphylococci*. While funding for the research for novel antibiotics is decreasing, it is imperative to identify and develop alternate treatment strategies to deal with this issue. Phage (bacteriophage) therapy is one method that is becoming more and more popular. The rapid development of resistance to antibiotics in *Staphylococcus aureus* is the main topic of this investigation. Phage therapy's potential in this situation is also discussed, as is its suitability for high-risk patients.

Keywords: *Staphylococcus aureus*, antibiotics, phage therapy, multidrug resistant bacteria, infections

Introduction:

Phage (bacteriophage) therapy was first suggested as an antibacterial remedy in the 1910s. The exponential rise in antibiotic-resistant strains has recently sparked increased interest in its potential to cure bacterial illnesses. Bactiophage (phage) therapy has become more and more popular as an alternative therapy for bacterial infections, particularly those caused by multidrug-resistant (MDR) bacteria. Bacteria are killed by phage treatment using lytic phages. During the lytic phase of infection, a phage exploits the cellular machinery of the host to replicate itself after inserting its genetic material directly into the desired bacterium. After cell lysis, host bacterial phage offspring are released, and a new cycle is initiated. The term "secondary infection" referred to the invasion of bacteria by the progeny released from lysed cells, whereas "primary infection" refers to the initial phage infection of bacteria. Targeting multidrug-resistant bacteria using bacteriophages that are specifically pathogenic can imitate the effects of an antibiotic agent and is known as phage therapy (PT) (1).

Microorganisms including bacteria, fungus, actinomycetes, and spirochetes can all be infected by the virus known as a bacteriophage (phage). Phage offers a lot of potential for preventing and controlling bacterial infections due to its strong specificity, low toxicity, good bactericidal activity, and good biological safety. Bacterial infections cause many health problems, but the issue was resolved after discovery of antibiotics. Due to unnecessary use of antibiotics, the bacteria have developed specific mechanisms to resist effects of antibiotics for example, the important worldwide bacteria *Staphylococcus aureus* (*S. aureus*) has developed methods for resisting the antibiotics that are now easily available. It might be possible to develop therapeutic agents that serve as antibiotic alternatives in the battle against antibiotic resistance. One of the most effective alternatives could be bacteriophages and bacteriophage-based products (2).

***Staphylococcus aureus*:**

The coagulase-positive, nonmotile Coccoid bacterium *Staphylococcus aureus* is a member of the Firmicutes phylum. With 52 species & 28 subspecies in the Staphylococcus genus, *S. aureus* is by far the one with the most clinical significance (3). *S. aureus* is present within the nasal mucosal commensal microbiota of 20–40% of the general population. *S. aureus* can transmit infection when the epidermal and mucosal barrier are disrupted, such as because of chronic diseases of the skin, wounds, or surgical operations. *S. aureus* can then penetrate into the tissues below or the bloodstream. People with surgical instruments that are invasive (such as periphery and central vascular catheters) or weaker immune systems are more susceptible to get *S. aureus* infection. *Staphylococcus aureus* is widespread among humans and in hospital settings (4). In the 1880s, Ogston made the initial discovery in the purulent pus of a leg abscess. Staphylococci are commonly found to be the source of bacterial infections in humans due to the rise of multidrug-resistant strains, and their management is challenging. Skin infections, endocarditis, osteomyelitis, pneumonia, and bacteremia are all brought on by *S. aureus*. *S. aureus* emerged as a significant factor in hospital-based medicine-related infections. The first anti-staphylococcal penicillin was created in 1960, and a year after it was used in a clinical setting for the first time, methicillin-resistant staphylococcal aureus (MRSA) emerged (5).

***Staphylococcus aureus* Genetic structure:**

There is only one circular, double-stranded chromosome and many plasmids in the *S. aureus* genome. Methicillin- resistant *Staphylococcus aureus* (MRSA) and methicillin sensitive *Staphylococcus aureus* (MSSA) have some similarities and differences (6). The genes involved in housekeeping and other metabolic processes may be found in the genomic core, It accounts for over 75% of the whole genome and is very similar in MRSA and MSSA strains. About 25% of the staph aureus genome is made up of mobile genetic components, including virulence factors, genomic plasmids, chromosome cassettes, transposons, and dynamics of antibiotic resistance (7).

Treatment of Infections caused by *Staphylococcus aureus* and Related Challenges:

Several antibiotic guidelines are currently developed for the treatment of infections caused by *S. aureus* and are continuously updated relying on epidemiological information regarding antibiotic resistance trends, national and international resistance surveillance, and effectiveness data of new anti-staphylococcal medicines (8). For specific infections like the skin and soft-tissue illnesses (SSTIs), bones and joint infections, a condition known as endocarditis, infections of the urinary tract, meningitis, and pneumonia, the guideline includes recommendations for both weak and strong antibiotics along with treatment plans (dosage and duration).

Clinical anti-infective therapy is getting more and more difficult as the prevalence of multidrug resistant *S. aureus* strains and rates of resistance increase. Bacteria's reduced capacity to absorb drugs is caused by decreased cell membrane permeability, which leads to antibiotic resistance. Due to its resistance to a variety of medications MRSA is a form of multidrug resistant "super bacteria" that is challenging to treat in clinical settings. The elevated levels of mortality and morbidity associated with MRSA infection, which pose a serious threat to people's health and have caught the curiosity of the international healthcare society. Due to antibiotic resistance, several novel medications, such as phage treatment, are required to treat infections brought on by MRSA (9).

Antibiotics Resistance:

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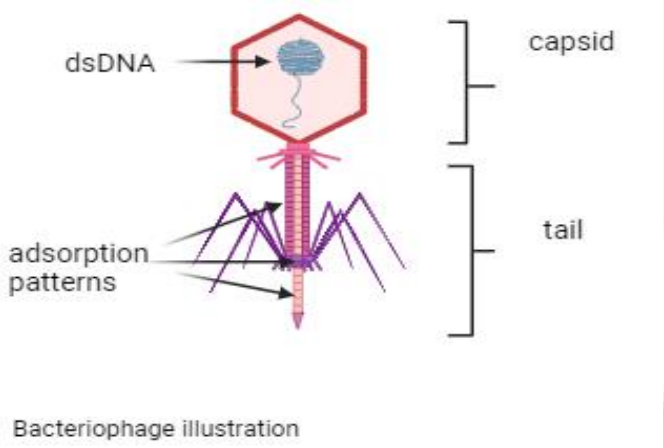
Reduced cell membrane permeability impacts the energy metabolism of these bacteria, the energy production of these bacteria is impacted by decreased permeability of the cell membrane, which also impairs medication uptake and results in antibiotic resistance (10). Reduced membrane permeability is a factor in *S. aureus*' resistance to aminoglycoside antibiotics, which ultimately leads to reduced drug intake. Two variables, including (i) the emergence of antibiotic resistance and (ii) virulence factors, affect a pathogen's capacity to transmit infection. *S. aureus* develops resistance by the acquisition of specific mobile genetic elements (SCCmec) harboring resistance genes, such as mecA producing the unique protein named penicillin-binding protein 2a (PBP2a) (11). It can therefore replace the biosynthetic activities of PBPs because of its poor affinity for beta-lactam antibiotics. In addition to SCCmec, mobile genetic elements like as transposons, plasmids, insertion patterns, integrons, integrative-conjugative factors and pathogenicity islands are also involved in the development of resistance. Transposons can migrate from one plasmid to another and even from the DNA of a chromosome onto a plasmid, which allows them to transmit resistance genes. A major proportion of *Staphylococcus aureus* infections is due to MRSA (National Nosocomial Infections. The term "transposons" refers to a class of mobile genetic components (12). Because antibiotic resistance develops quickly when antibiotic therapy fails, outbreaks of various drug-resistant strains frequently affect both the general public and medical settings. This is due to the development of genes encoding antibiotic resistance from various *S. aureus* strains or even from other genera. MRSA strains produce β lactamase which results in reduction of effectiveness of antibiotics that leads to Methicillin resistance *Staphylococcus aureus* to antibiotics (13).

Phage Treatment:

The word "phage" refers to a group of viruses that may invade and kill bacterial cells. Early throughout human history, its potential was recognised (14). Because a bacteriophage has a head that holds RNA or DNA and an extended tail that is used to insert its genome into bacterial cells, it has a unique morphological shape. Its fewer receptors on the eukaryotic cells make it unlikely to penetrate mammalian cells, making it the most potential substitute treatment approach for treating human being.



Bacteriophage illustration

Due to an increase in the prevalence of multidrug-resistant bacteria in worldwide infections, antibiotic administration for treating diseases caused by bacteria has encountered exceptional difficulties in recent years. The rise of several bacteria that are resistant to drugs, including Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus faecalis TB and particularly MRSA, has resulted in substantial improvement in phage research. Phage preparations have faster self-replication, higher specificity, and shorter development times than antibiotics (15). One of the most promising treatments for human diseases, particularly types resistant to antibiotics, is phage therapy. As far back as 1921, phages were used as therapy for staphylococcal infections of skin. The benefits of phages have gained increasing academic attention as drug-resistant bacteria have become more prevalent. Estrella and colleagues showed that numerous staphylococci strains carried bacteriophages, despite the fact that most attention has been paid to using phage to treat Gram-negative bacteria. Some strains could be lysed by these phages (16). However, by subjecting staphylococci to a variety of phages, a pattern of susceptibility can be discovered and differences or similarities across isolates can be identified. In patients with persistent infections brought on by polymicrobial agents, phage treatment (PT) should also be carefully evaluated. The researchers discussed the likelihood of anti-*S. aureus* PT's insufficient protection against pathogens other than staphylococci. Additionally, while using PT to treat infections in cancer patients, extra vigilance should be taken (17). T4 and M13 bacteriophages were introduced into prostate cancer cell lines (PC-3) and resulted in the overexpression of integrins, which may benefit prostate cancer patients. Other malignancies, like ovarian and breast cancers, could suffer because of it. The proliferation of these cancer cells and their ability to survive would be enhanced by the overexpression of particular integrins (ITGAV and ITGB3) (18).

Conclusion:

The bacterium *Staphylococcus aureus* is abundant in the environment and can be found on the skin surface and in the mucosa of the URT (upper respiratory tract) in humans. *S. aureus* is a significant human pathogen even though 20% of the population is a long-term carrier and most persons do not exhibit clinical signs. *S. aureus* has become the most widespread pathogen in hospitals around the world and causes infection in both hospitals and populations. The British bacteriologist Fleming developed penicillin in the 1840s, and it was applied clinically to treat *S. aureus* infections. This study summarizes the key elements of the observed *S. aureus* antibiotic resistance that need to be addressed and comprehended to help phage therapy become a common clinical treatment. Overall, this assessment reveals a number of things. First off, the successful use of phage/antibiotic combinations against numerous multidrug-resistant bacteria is supported by the favorable interactions between phages and antibiotics. In order to justify clinical trials, establishing the efficacy would be essential of such a combination treatment in the appropriate in vivo models. Thirdly, given that each phage formulation demonstrates distinct pharmacodynamic features, study is badly needed to determine how phage formulation's function. However, the encouraging results provide great incentive to continue testing with phage/antibiotic combination & increase the likelihood that an antibiotic substitute may soon be realized.

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Table 1 A short overview of how *Staphylococcus aureus* infections are treated with phage and phage-related medicines.

Bacterial pathogen	Phage source	Clinical condition	Phage preparation	Phage doses (PFU/ml)	Number of dose	Routes of administration	Treatment duration	Clinical outcome	References
MSSA	Pherecydes Pharma	Infection related to medical devices (knee prosthetic)	Phage Cocktail	1 ×10	Only single dose	Local	NA	Improved clinically	Ferry et al., 2020
MSSA	Eliava Institute	Diabetic foot osteomyelitis	Single Phage	NR	Multiple doses	Local	7 weeks	Resolved	Fish et al., 2018
MSSA	Biopreparations LTD Eliava	Osteomyelitis	Phage Cocktail	1 ×10^7	Multiple doses	Local and oral	5 weeks	Resolved	Nadareishvili et al., 2020
S. aureus	Hindu University of Banaras	Chronic wound	Phage cocktail	1 ×10^9	Multiple doses	Local	13 days	Resolved	Gupta et al., 2019
MSSA	AmpliPhi Biosciences	Device-related infection	Phage Cocktail	3 ×10^9	Multiple doses	Intravenous	4 weeks	Resolved	Aslam et al., 2019
MRSA	Therapeutics for Adaptive Phages Sanubiom	Chronic rhinosinusitis	Single phage	1 ×10^9 1 ×10^10	Multiple doses	Local	3 weeks	Resolved	Rodriguez et al., 2022