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A Concise Overview of Bacteriophage: An Alternative to Antibiotics

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Abstract

This paper relates a concise overview of bacteriophage to serve as an alternative to antibiotics. Antibiotics are meant to kill or inhibit bacteria threatening humans or related biota. Bacteria are able to affect humans or biota due to ability to incite infections. The discovery of antibiotics has been considerably of important to modern medicine until recently when resistance is developing due to evolution and other prevailing forces (such as misuse, abuse, massive use, etc). Therefore, seeking alternative against infectious bacteria is imperative. Phages are viruses that kill bacteria. They are supposed candidates to kill bacteria and combat resistance to antibiotics. The phages are able to specifically invade bacteria, hijacked the host replicating machine, instruct the phage DNA replication, elicit lysis to release upcoming phages. This kills the hosting bacteria. The phages are specific, numerous, and effective. Their use should be enhanced for mankind benefits.

Keywords; Phage, Bacteria, Antibiotics, Infection, DNA

Introduction

Bacteriophages are numerously inhabiting in the biosphere, about 10-fold of more than the bacterial species, phages are around. The phages also behave inherently in human microbiome, therefore beneficial in therapeutic purposes (Garba et al., 2024; Romereo-Calle et al., 2019). Promisingly, phages are out there to save the world from the burning fire of antibiotics resistance escalating nowadays. Resistant bacteria serve as a thorn threat affecting humans and other biota and hurdling the attempt to curb infectious diseases (Romereo-Calle et al., 2019; Sarkingobir et al., 2022). Post antibiotics era is upcoming, causing minor injuries to lead to devastations, and additionally the world suffering from infections. Parable, *Enterococcus faecium, Kblebsia pneumoniae, Enterobacter spp, Acinetobacter baumannii* are typically strongly resisting antibiotics, therefore escalating infectious effects (Megha et al., 2024). About 700, 000 persons are dying due to antimicrobial ineffectiveness. The number will potentially escalate later (Megha et al., 2024). Increased utilization of antibiotics spurred resistance in bacteria, in turn spurring contemporary drug regimens to be ineffective for the meant purposes (Lusiak-Szelachowska et al., 2022; Khamdneh et al., 2021). Phages are newly introduced to curb the effects of resistance. Phages are viruses that potentially infect and kill bacteria. They are present day efficient tools that can substitute antibiotics against bacteria (Megha et al., 2024). This paper relates a concise overview of bacteriophage to serve as an alternative to antibiotics.

Antibiotics Resistance Threatening the World

Bacteria are microscopic in size organisms that inhabit our environment (such as soil, water, human body). Albeit, bacteria are useful, some of them impose danger upon our health causing infections, injuries, and deaths (Dutta et al., 2021).

An antibiotic includes either synthetic or natural material utilized to kill or inhibit bacterial growth. Antibiotic may destabilize cell wall, rupture membrane, affect protein synthesis, affect genetic material synthesis, or use other mechanistic ploy to exact it's actions (Arsene et al., 2022). Antibiotics resistance, is however, an inability of antibiotics to exert their actions. Antibiotic resistance may be achieved due to devised adaptations such as antibiotic modification, enzyme degradation, alterations of membrane permeability, metabolic alterations, and horizontal gene transfer escalate resistance (WHO, 2015). The ability of bacteria to adapt to the destructive usual action of antibiotics substances is termed as resistance (Dutta et al., 2021; Arsene et al., 2022). Some leading diseases that are escalating due to bacterial resistance include pneumonia, urinary tract infections, gonorrhea, wound infections, and blood transmitted infections, among others (Mobarki et al., 2019).

"Most commercial antibiotics are naturally produced by fungi or bacteria as part of their repertoire of secondary metabolites. Perhaps most well know is the production of penicillin by the *Penicillium* mold, but most of our commonly used antibiotics, among them streptomycin and tetracycline, are products of soil bacteria belonging to the genus *Streptomyces*. The role of secondary metabolites, and thus the natural function of antibiotics, is not well understood. These small molecules are produced by microbes under certain circumstances, and are not involved in the growth and reproduction of the organisms in an obvious way. A common theory is that antibiotics are exuded to combat surrounding microbes that compete for the same local resources, and there are studies showing that bacteria inhibit growth of their neighbors under certain circumstances. In other cases, antibiotics have been found to affect cellular transcriptional responses, and they could thereby be acting in the capacity of signaling molecules, regulating interactions and responses within bacterial communities" (Albretcht, 2018). "It has recently been suggested that antibiotics in fact are part of the physiological function of the producing organism by being involved in regulation of the cellular growth rate. Regardless of their original purpose, antibiotics have functioned as "wonder drugs" in the treatment of human and animal infections for decades" (Albretcht, 2018).

Introduction about Bacteriophages

Phages are the prevalent beings known on earth surface (Moorlag, 2023). They are 10 times more than bacteria in terms of occurrence. Certainly, the word "bacteriophage" was brought from "bacterio" meaning "bacteria," and "phage" meaning "eater." It is therefore literally important to say, bacteriophage refers to "bacteria eater" because the phage have the ability to destroy bacteria host cells. Every bacteriophage contains a nucleic acid entity encircled by a proteinous structure (Pundir, 2020). Phages are specialized in their ability of infecting a host bacterial cell and in turns resulting in its destruction by taking over the host cells metabolic dealings (Moorlag, 2023). The diverse genetic diversity of phases gotten due to their large numbers encouraged them to live and evolve along with the host diversity (Moorlag, 2023).

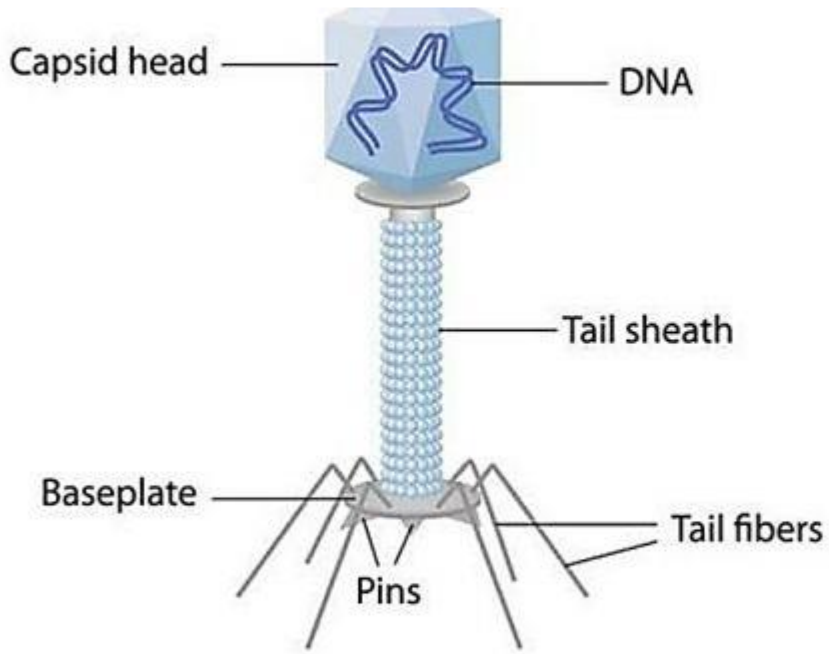


Figure 1; Bacteriophage structure, Source: Ahmed & Ahmed (2022)

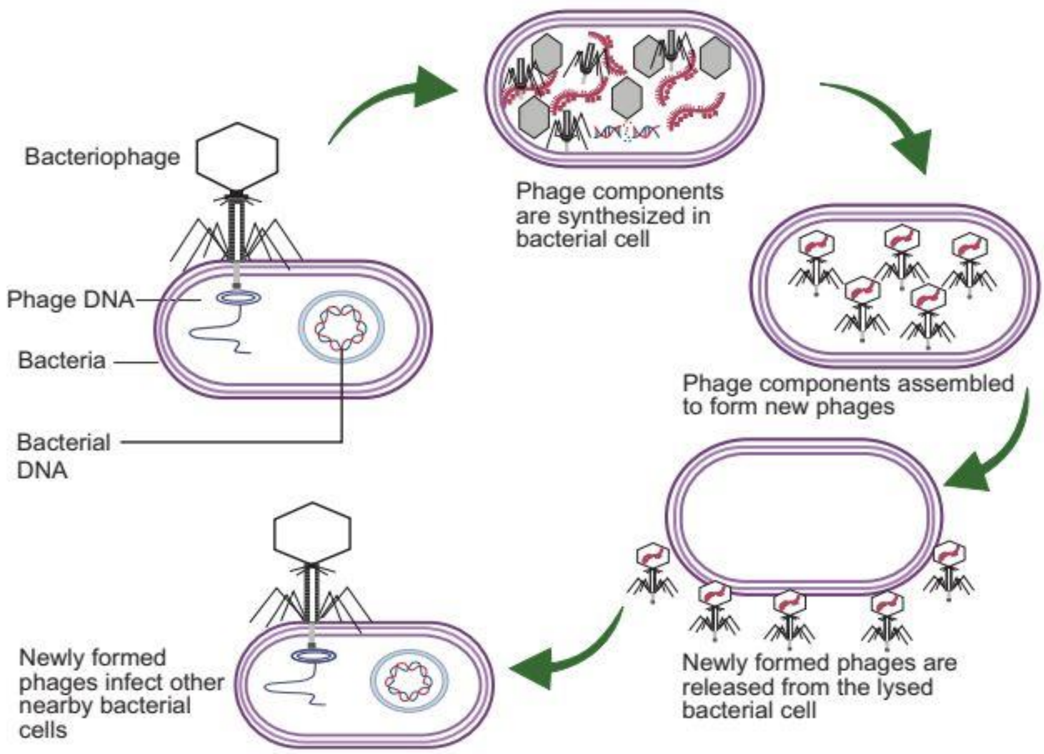
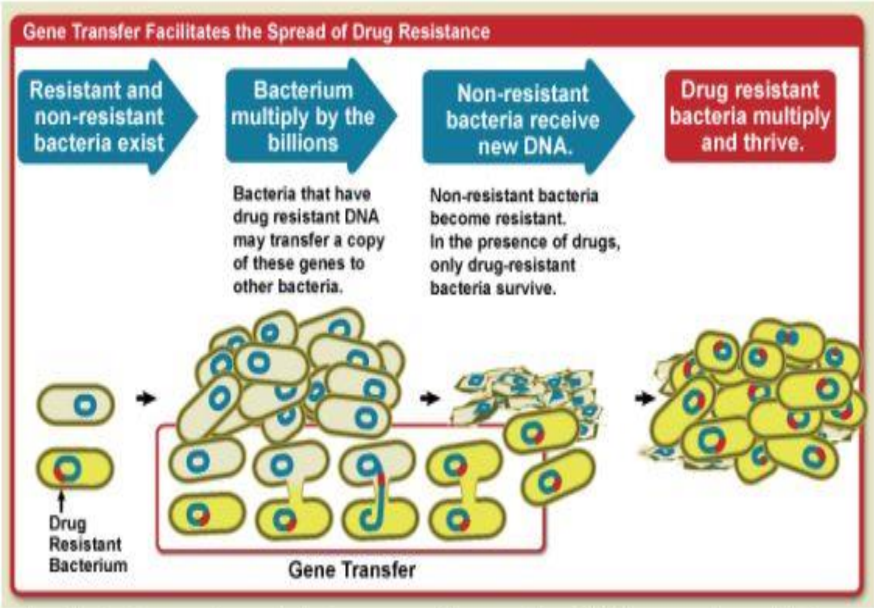


Figure 2: Phages mechanism of infection inducement; Source: Fowoyo, (2024)



When two bacteria come in contact, they can easily pass along DNA segments containing antibiotic-resistant genes (red segments). (Adapted from the National Institute of Allergy and Infectious Diseases.)

Figure 3: Bacteria obtained DNA to facilitates antibiotic resistance; Source: WHO, (2015)

Table 1: Some antibiotics against bacteria

Class	Examples	Binding site	Mechanism of action
Aminoglycosides	Gentamicin Kanamycin Streptomycin	Ribosome	Inhibit protein synthesis
Amphenicols	Chloramphenicol	Ribosome	Inhibit protein synthesis
Ansamycins	Rifampicin	RNAP	Inhibit RNA synthesis
Beta-lactams	Carbapenems Cephalosporins Penicillins	PBPs	Inhibit cell wall synthesis
Glycopeptides	Vancomycin	Peptidoglycan	Inhibit cell wall synthesis
Lincosamides	Clindamycin	Ribosome	Inhibit protein synthesis
Lipopeptides	Daptomycin	Membrane	Disrupt cell membranes
Macrolides	Erythromycin	Ribosome	Inhibit protein synthesis
Oxazolidinones	Linezolid	Ribosome	Inhibit protein synthesis
Sulfonamides	Sulfamethoxazole	DHPS	Inhibit folic acid synthesis
Tetracyclines	Tetracycline	Ribosomes	Inhibit protein synthesis
Polymyxins	Colistin Polymyxin B	Membrane	Disrupt cell membranes
Quinolones	Ciprofloxacin Nalidixic acid	Topoisomeras- es	Inhibit DNA replication
Others	Fosfomycin Fusidic acid Trimethoprim	MurA EF-G DHFR	Inhibit cell wall synthesis Inhibits protein synthesis Inhibit folic acid synthesis

Source: Albrecht, (2018)

Phages Life Cycles

Phages follow a development pattern that may be depicted as a cycle. The life cycle of phage involved event series that occur from the attachment of phage upon the bacteria and resultant release of daughter phage entities. This lytic cycle occurs in five stages involving, adsorption, penetration, transcription and translation, as well as assembly and exit (Adebayo et al., 2017).

The other cycle called the "lysogenic" require replication of phage nucleic material in tandem with the host cell over various generations; without necessarily showing major metabolic problem to the host cell. This type of cycle is rare, and on many occasions, the phage may transgress to follow the lytic cycle (Adebayo et al., 2017).

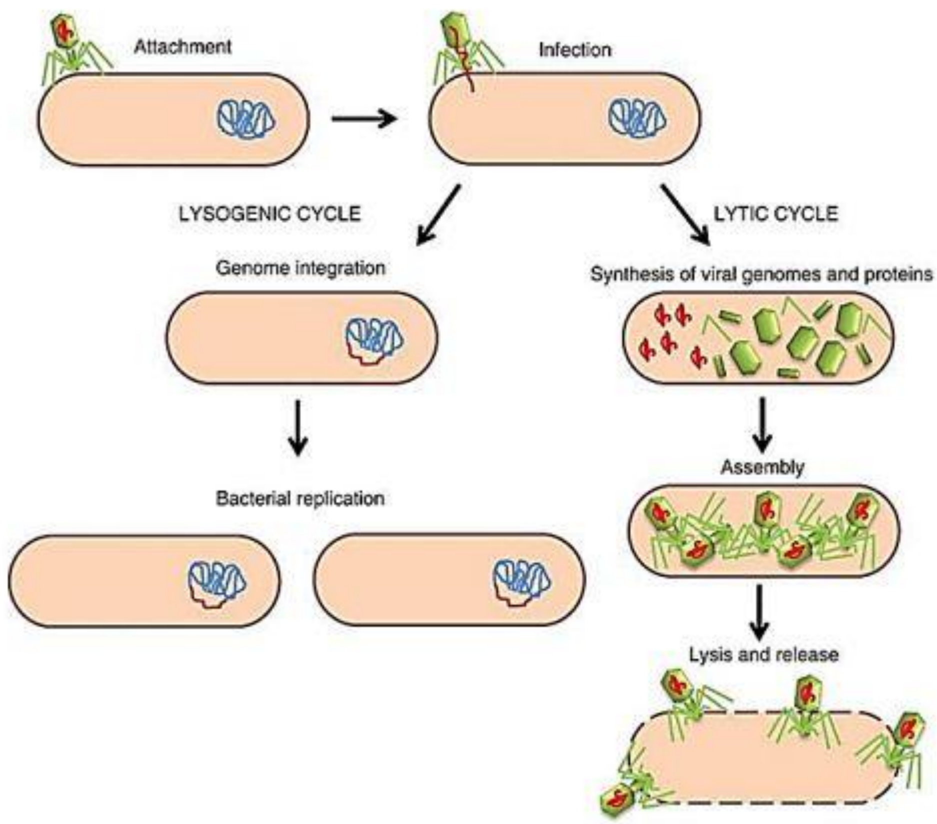


Figure 4: Life cycle of a bacteriophage, Source: Ahmed & Ahmed (2022)

Phages Pharmacology

Phages may be administered using passive or active therapeutic methods. Actively, phages are produced at low concentration to the bacteria to rely on the lytic release of progeny for therapeutics. This can be a promising intervention for disease more than the antibiotics cure. Whereas, passive treatment with pages include a single or multiple rounds of administration of sufficient amount of phage to cure bacterial disease. Fewer units of phages are needed to cure bacteria better than the antibiotics. It was asserted that, degradation of phages by body's immune system could not produce toxic byproducts contrary to antibiotics treatment. This behavior of low toxicity could be due to the simple content of the phages (Pundir et al., 2020; Ahmed & Ahmed, 2022). Pharmacokinetically, phages could be clinically administered parenthetically coupled with doses orally, topically, and aerosolization (Romero-Calle et al., 2019).

Steps in Phages Therapy

A phage therapy must follow some protocols from screening (isolation), production, purification, storage and formulation and administration (Moorlag, 2023).

Instances of Phages

Studies in animal indicated that phase could be used to treat diarrhea due to *E. coli,* phages were shown to treat *Acinetobacter baumanii, S. aureus*, *P. aeruginosa* in animals. Reports show potential of phages to treat food borne infection by *Salmonella spp., Campylobacter jejuni,* and *E. coli*. Likewise, attempts to treat respiratory disease in animals indicate that, there was an important improvement (Adebayo et al., 2017; Khalid et al., 2020).

Nevertheless, bacteriophages have been utilized in therapeutic means in humans over the years. Greatly, phages were utilized in treatment of skin diseases and other skin problems such as burns, wounds, ulcers, diabetic ulcers. This was done after World War Two in Eastern Europe. A multidrug resistant to *P. aeruginosa* was positively treatment with phages. It was similarly reported that; oral phage administration was useful in treatment of cholera. Other human cases of potentially utilizing phages include, treatment of cystic fibrosis, respiratory tract infections, diarrhea (Adebayo et al., 2017; Khalid et al., 2020).

Therapeutic Role of Bacteriophage

Phages utilized in therapy with the sole aim of combating bacteria, such as lethal cases of *E. coli*, *V. cholerae, Salmonella spp*., and *S. aureus* infections. Phages could be administered orally, topic ally, and locally into tissues or through systemic circulation (Adebayo et al., 2020). Sometimes an infected cell could be utilized to deliver phages to the affected cells using right concentration to bring about desired effects (Adebayo et al., 2020).

Phages are Advantageous Over Antibiotics

There are some unique features of phages that make them more favorable compared to antibiotics. There are examples of phages advantages below:

- Bactericidal agents- There is wide knowledge that, cell infected by phage never regain viability, which is in contrast with the antibiotics resistance
- Minimal disruption of normal Flora-Phages exhibit host specificity; therefore, affect not the normal cell flora, instead display specific actions upon strict range of bacteria, in contrast to antibiotics with broad spectrum actions
- Auto "dosing"-Phages upon lysing the host cell have the potential to increase numbers and affect host cells
- Rapid discovery- Phages are easily discovered and isolated for therapy purposes compared to some antibiotics (Ahmed & Ahmed, 2022).
- Biofilm clearance ability -Biofilms made by bacteria are complex and acquire tendency to resist many antibiotics. However, the advent of phages avails that limitation of antibiotics due to the capacity of phages to infiltrate biofilms and scatter them (Adebayo et al., 2017).
- Low toxicity - Due to low or simple contents of phages, involving a nucleic acid molecule and a housing make phages very low in toxicity; in contrast with antibiotics (Romero-Calle et al., 2019; Pundir, 2020).

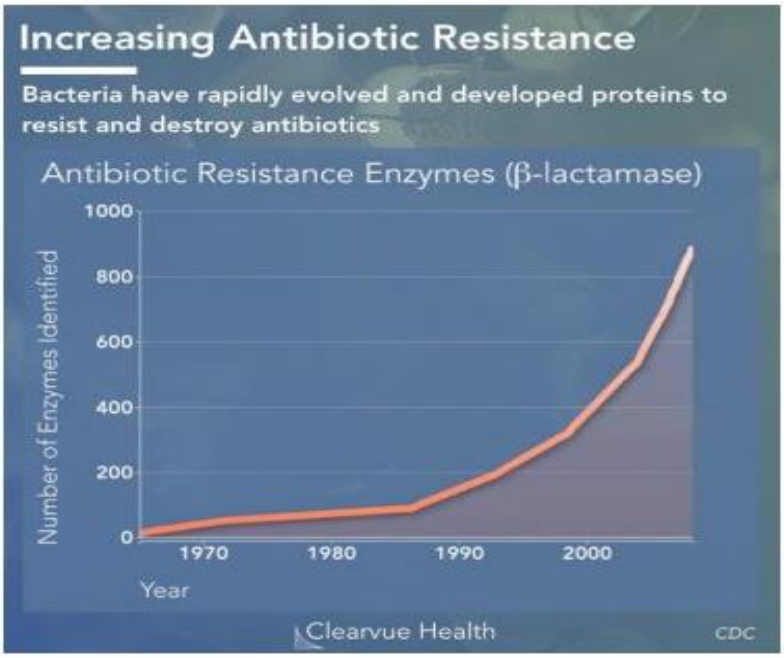


Figure 5: Trend in antibiotics resistance; Source: Moorlag, (2023)

Table 2: Advantages of bacteriophages over antibiotics

Delivery Route	Advantages	Disadvantages	Mitigations to Hurdles
Intraperitoneal	Higher dosage volumes possible. Diffusion to other sites.	Extent of diffusion to other sites may be overestimated in humans (most data from small animals).	Multiple delivery sites.
Intramuscular	Phages delivered at infection site.	Slower diffusion of phages (possibly). Lower dosage volumes.	Multi-dose courses. Multi-dose courses.
Subcutaneous	Localized and systemic diffusion.	Lower dosage volumes.	Multi-dose courses.
Intravenous	Rapid systemic diffusion.	Rapid clearing of phages by the immune system.	In vivo selection of low-immunogenic phages may be possible.
Topical	High dose of phages delivered at infection site.	Run-off from target site if phages suspended in liquid.	Incorporate phages into gels and dressings.
Suppository	Slow, stable release of phages over long time.	Limited applications/sites. Risk of insufficient dosing. Technically challenging to manufacture.	Careful consideration of phage kinetics required.
Oral	Ease of delivery. Higher dosage volumes possible.	Stomach acid reduces phage titer. Non-specific adherence of phages to stomach contents and other microflora.	Add calcium carbonate to buffer pH. Microencapsulation to deliver phages to target area.
Aerosol	Relative ease of delivery. Can reach poorly perfused regions of infected lungs.	High proportion of phages lost. Delivery can be impaired by mucus and biofilms	Use of depolymerases to reduce mucus.

Source: Romero-Calle et al., (2019)

Some Potentials of Bacteriophages

The potentials of bacteriophages in various therapeutic actions were evaluated in some study cases as shown below:

- A study involved a man admitted at a hospital for problems including sepsis was treated with phage, at the end, the patient exhibited improves kidney function.
- Treatment in respiratory infections using phage demonstrated possibility of active effects of phages in respiratory therapy
- Patient suffering from chronic ear infection were examined, and result indicated benefits to the affected patients
- Treatment of leg ulcers using phage has passed phase 1, therefore needs phase 2 for further evaluation.

- Treatment of diarrhea in children shows no adverse effects on children treated orally with phage
- Phage therapy for acne, eczema, ulcers, had been underway to complete development
- Phages are being made to treat crop diseases and prevent food contamination
- Phages for livestock treatment were been brandished in China. Other area of phage contribution include aquaculture (Romero-Calle et al., 2019).

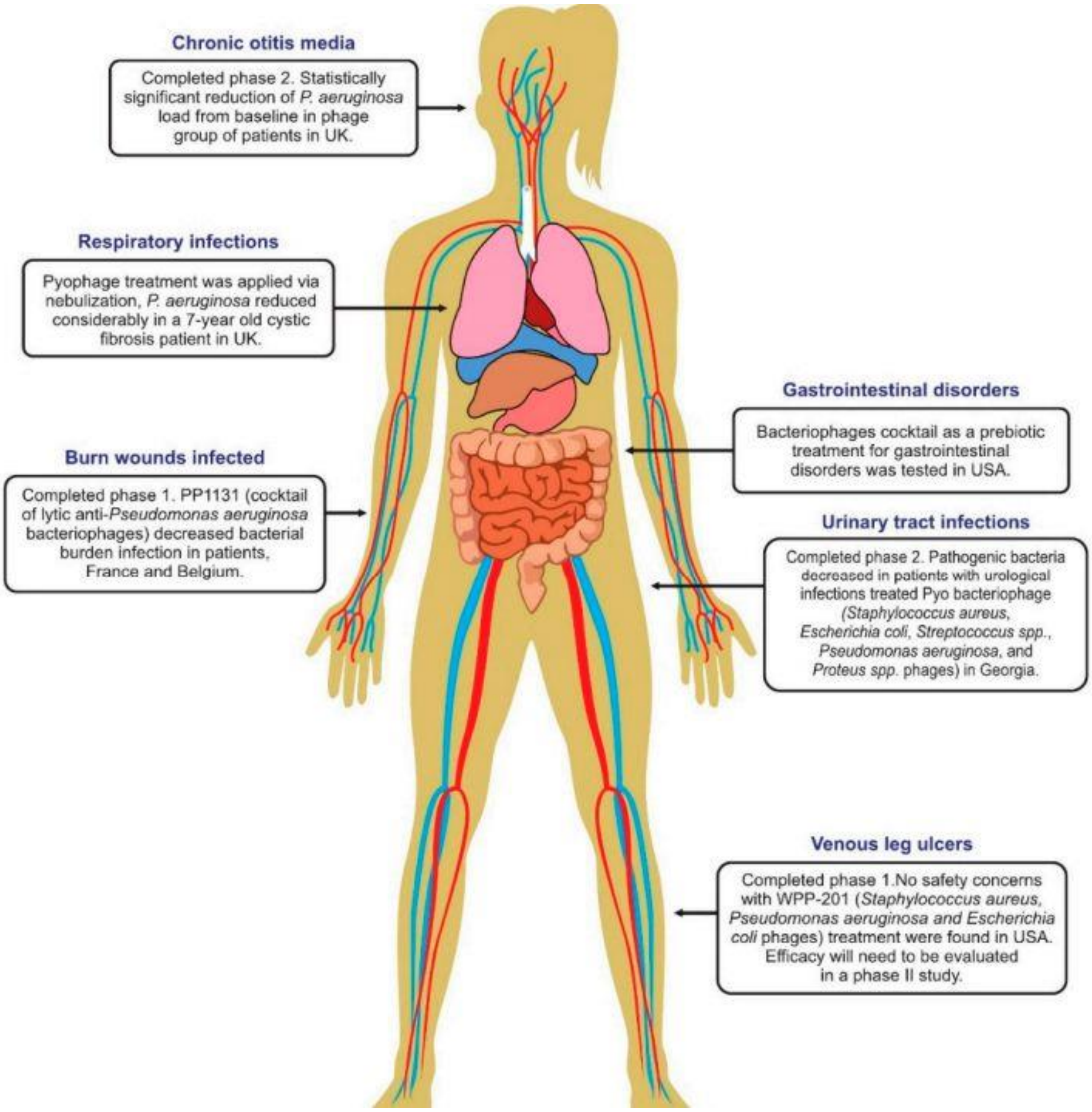


Figure 6: Phages trials underway; Source: Romero-Calle et al., (2019)

Mechanism

Phage initiates infection of the host through lytic phages. Involving binding upon certain receptors from the surface of the hosting bacteria. Thereafter, the phages proceed by divulging its genetic content into the hosting cell (Mobarki, et al., 2019). The cell (phage) take over the replication tool of the hosting cell in order to produce succeeding progeny phages. Thereafter, successive replication spurs lysis, therefore killing the hosting cell, and consequently divulging the newly synthesized viruses (phages) (Fowoyo, 2024).

Hurdles On the Tract and Efforts for Remedy

There are a quite number of perceived challenges that may affect phages utilization. One of the major thing is, there is absence of randomized trials in most cases to oversee phage uses, as opined by Fowoyo (2024). Time consumption in phage therapy development that, may involves selecting of suitable phage-to-host candidates. Possibly, the internal immunity in biota may perceived phages as xenobiotics and act upon them (Fowoyo, 2024). Patients and public awareness, interest, and attitude perceptions on phage are not well vast by the present data available. This may induce hurdles in the application of phages in therapeutic means.

To remedy the situation, there are certain attempts or suggestions provided by pro-phages adherents. There is need for updated data, that provide all needed awareness to experts, and as well the public. Regulatory commitments are essential from all the stakeholders' agencies around the world concerning phage therapy (Ssekatawa et al., 2021). Intensified, vast, and extensive research and academic discourse pertaining phages should be supported, as well facilitated (Fowoyo, 2024).

Conclusion

Bacterial infections are causing morbidity and mortality every day, despite the administration of antibiotics. Misuse of drugs, adaptation, drug abuse, massive usage, are among the leading reasons for antibiotic resistance nowadays. Thus, searching for a new solution is activated. Among other things, phages are viruses that infect and kill bacteria specifically and simply, thus, the need for its broach. Bacteriophages are a new trend with promising future of combating antibiotic resistance of nowadays.

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