The appearance of resistances in bacteria is an evolutionary phenomena, although the excessive exposure to antibiotics makes it a growing problem. There is a group of bacteria called ESKePe, which comprises Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Pseudomonas aeruginosa species, that is very problematic in community and hospital settings due to their resistance to multiple antibiotics; they have been considered by the Infectious Diseases Society of America (IDSA) as priority targets for antimicrobial research.

The increase and continuous spread of resistances lead to the necessity of new compounds for the treatment of bacterial infections. However, there has been a lack of new antibiotics since the 1980s. This fact and the appearance of new antibiotic-resistant bacteria has encouraged the search of new techniques to solve the problem. Bacteriophages are proposed as a potential tool for treating infectious diseases as they are bacterial viruses that replicate exponentially until the death of bacteria.

Objective: To perform a comparative analysis (critical points of phage therapy and advantages in front of antibiotics) and show some examples of phage therapy.

**COMPARATIVE ANALYSIS**

**CRITICAL POINTS OF PHAGE THERAPY**

**Toxicity**

-Septic Shock
-Septic Shock Syndrome

**Phage choice**

1. Individual phage chosen by isolation of infectious pathogens
2. Cocktail of phages

**Phage manufacturing**

- Bacterial toxin removal
- Formulation
- Quality control

**Interaction with non-target tissue**

Phages can interact with non-target tissue, although these interactions do not produce side effects.

**Efficacy**

Just few bacteriophages are efficient as therapeutic agents.

**Bacterial resistances to bacteriophages**

Bacterial resistances can appear by many mechanisms:

**Avoidance**

- cocktail of phages or phage + antibiotic

**EXAMPLES OF PHAGE THERAPY**

**Example 1**

- **Bacteria**: S. aureus
- **Bacteriophage**: φM11
- **Organism**: mice
- **Result**: 80% untreated mice died within 24 hours post-infection
- **Mice**: treated instantly after infection were protected.
- **Immune response not implied**

**Example 2**

- **Bacteria**: P. aeruginosa
- **Bacteriophage**: cocktail
- **Infection**: chronic otitis
- **Organism**: adult humans
- **Result**: decrease in Pseudomonas loads

**Example 3**

- **Bacteria**: vancomycin-resistant E. faecium
- **Bacteriophage**: EN66
- **Organism**: mouse model
- **Result**: administration between 45 minutes and 5 hours after the infection saved all mice.

**Example 4**

- **Bacteria**: Salmonella enterica
- **Bacteriophage**: cocktail
- **Organism**: chicken and mice
- **Result**: reduction of bacteria was obtained when animals were treated frequently and especially, before the infection of Salmonella

**Other example**

- **Bacteria**: Salmonella enterica
- **Bacteriophage**: cocktail
- **Organism**: chicken and mice
- **Result**: reduction of bacteria was obtained when animals were treated frequently and especially, before the infection of Salmonella

**Materials & Methods**

**Figure 1:** Phage therapy requires the presence of infective bacteria in a patient and bacteriophages that kill this bacterium species. Bacteriophages are administrated to the patient (the way of administration depends on the infection). Bacteriophages arrive to bacteria and start their cycle. They replicate and provoke bacterial lysis. Then, the released bacteriophages can infect other bacteria and repeat the process.

**Figure 2:** Cellular toxins (IPS: Lipopolysaccharide, 5A: superantigen) can be released during cell lysis and provoke systemic inflammatory responses and increase morbidity and mortality. Modified from [1].

**Figure 3:** Cocktail of bacteriophages. The use of different phages simultaneously allows targeting a wider number of bacterial species. Modified from [1].

**Figure 4:** Modification of bacteriophages by (a) directed evolution or (b) addition of a coat, so as to avoid the inactivation and clearance. Modified from [1].

**Figure 5:** Bacteriophage manufacture has multiple steps: production, purification, formulation, quality control, among others. The process is complicated as the cell lysis releases endotoxins and other cellular toxins and by the need of multi-phage cocktails. Modified from [1].

**Advantages**

**Table 1:** Comparison between antibiotics and bacteriophages

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antibiotics</th>
<th>Bacteriophages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Host specificity</strong></td>
<td>Broad</td>
<td>Narrow</td>
</tr>
<tr>
<td><strong>Solved infections</strong></td>
<td>Difficult infections are not solved</td>
<td>Difficult infections: biofilms, persister, antibiotic resistant bacteria</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Affect normal microflora</td>
<td>No serious but possible release of endotoxins</td>
</tr>
<tr>
<td><strong>Concentration in time</strong></td>
<td>Decrease Eliminated from the body</td>
<td>Self-regulating tools</td>
</tr>
<tr>
<td><strong>Synthesis</strong></td>
<td>Synthetics or semisynthetics</td>
<td>Ecologically pure</td>
</tr>
<tr>
<td><strong>Isolation and characterization of new phages</strong></td>
<td>Slower and more expensive</td>
<td>Faster and cheaper</td>
</tr>
</tbody>
</table>

**References**