Bacteriophages for Treatment of Bacterial Infections

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Bacteriophages: An introduction

Bacteriophage (phage) - a group of viruses that infect only bacteria, including pathogenic microorganisms

Bacteriophage T4

[Diagram showing the structure of Bacteriophage T4 with labels: Head containing DNA, Collar, Sheath, Base plate, Tail fibres]
Bacteriophages: An Introduction

Bacteriophage attach to its target bacteria, injects its DNA through the phage tail into the host cell

Phage directs the host cell to produce progeny phages at an exponential growth rate

Newly formed phage burst from the host cell, and infect new host bacteria until all traces of the bacteria is eradicated
History of Phage Discovery

• Frederick Twort was the original discoverer in 1915 of bacteriophages

• Felix d'Herelle is jointly credited with the discovery of bacteriophage along with Frederick Twort
World experience in past

- Commercial department at the Pasteur Institute (5 preps)
- German Bacteriophage Society (dried phages in tablet forms)
- German company Antipiol (Enterofagos)
- Eli Lilly Company (USA) (7 products based on phages)
- Swan-Myers of Abbot Laboratories
- Squib and sons (now belongs to Brystol Myers Squibb)
- Parke, Davis and Company (now part of Pfizer)
## Overall comparison of bacteriophages and antibiotics: Ability to overcome resistant bacteria

<table>
<thead>
<tr>
<th><strong>Antibiotics</strong></th>
<th><strong>Bacteriophages</strong></th>
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<tbody>
<tr>
<td>Antibiotics are unable to adapt to bacteria which has acquired resistance</td>
<td>Bacteriophages evolve alongside the bacteria due to the process by which they destroy the bacteria</td>
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<td>New classes of antibiotics must be elaborated, but eventually bacteria will become resistant to those antibiotics as well</td>
<td>Bacteriophages can be either selected to adapt to resistant bacteria in the event of new bacterial strain</td>
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<td>Phage cocktails can be used to exclude appearance of resistance</td>
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Overall comparison of bacteriophages and antibiotics: side effects

**Antibiotics**

- Wide range of adverse effects
- Elevated risk of allergic reaction
- Decline in efficacy as a result of increased resistance from bacteria
- Increased danger of side effects in immune-compromised patients

**Bacteriophages**

- There have been no reported side effects on humans in over 90 years of treatments
- **Bacteriophages** are completely harmless to humans, animals or plants
- As a result, there is no danger of over dosage with **Bacteriophages**
Eliava Institute

• 1916 – Tiflis Pasteur station was transformed to the Central Bacteriological Laboratory
• 1918 – George Eliava became a director of CBL
• 1923 - Inst. Bacteriology has been established by G. Eliava on the base of CBL
• 1930, 1931 - Felix d'Herelle was working at the Institute in Tbilisi
• 1937 – G. Eliava was executed
Staph phage against *S. aureus (MRSA)* strains

*In vitro* screening: 467 MRSA from the UK collection -98.5%

54 MRSA and 38 toxin-producing (not MRSA) from German Strain and Culture collection (DSMZ) – 99%

56 MRSA from NYU – 95%

100 MRSA from Royal College of Surgeon (Ireland) – 97%

Phages against β-lactamase–producing *E. coli* and *Klebsiella*

100 *E. coli* from Royal College of Surgeon (Ireland)
41 *E. coli* and 9 *Klebsiella* from Balgrist University Hospital (Switzerland)

Pyophage, Intestiphage, SES, Encophage, lab phages were tested


Pyo-Phage *(Staphylococcus, E. coli, Streptococcus, Pseudomonas, Proteus)*

Intesti phage *(Shigella, Salmonella, entero-pathogenic E. coli Proteus, Enterococci, Staphylococci and Pseudomonas aeruginosa)*

Enkophage *(Salmonella spp., Shigella spp., entero-pathogenic E. coli, Staphylococcus spp.)*

SES phage *(Staphylococcus spp., Streptococcus spp., E. coli)*

Fersis *(Staphylococcus spp., Streptococcus spp.)*

Staphylococcal monophage
Eliava Phage Therapy International Center

Urologist
Gynecologist
Pediatrician
Infectious disease specialist
Therapeutist
Eliava Phage Therapy International Center

(2014-2015)

- **3422** visits for phage treatment
- Phage preparations were sent to **427** patients abroad
- **37** Foreign Patients were treated, (France, USA, Romania, Canada, Norway, Denmark, China, Bulgaria, Italy, Germany, Austria, New Zealand, Lebanon, Russia, Uruguay)
- **24** Foreign patients (treatment on distance)
### Frequently occurring diseases in our clinic:

<table>
<thead>
<tr>
<th>Urologic diseases</th>
<th>Prostatitis</th>
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<tr>
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<td>Urethritis</td>
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<tr>
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<td>Cystitis and other inflammatory diseases of the urinary tract</td>
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<tr>
<td><strong>Gynecological Diseases</strong></td>
<td>Vaginitis</td>
</tr>
<tr>
<td></td>
<td>Colpitis</td>
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<tr>
<td></td>
<td>Other inflammatory diseases</td>
</tr>
<tr>
<td><strong>Internal medicine and Pediatrics</strong></td>
<td>Gastrointestinal tract diseases: gastroduodenitis, enteritis, colitis, irritable bowel syndrome, and others that cause frequent diarrhea or constipation</td>
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<td>Respiratory system diseases: sinusitis, bronchitis, bronchiectasis</td>
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<td>Cystic fibrosis</td>
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<td>Skin and soft tissue diseases</td>
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Clinical application

Case 1: Acute infection

Patient: T. K., 6 months old, female (Georgia)
Diagnosis: Antibiotic-associated diarrhea
Complaints: defecation 8-10 times a day, heavily sweating, deficit in gaining of weight, hyperkinesia of muscles on face
Bacteriological analyses: *Proteus mirabilis*, hemolytic *E. coli*
Conventional treatment: probiotics, antibiotics. Defecation increased until 10-12 times a day, green, smelly
Susceptibility: Pyophage, Ses-phage

Phage treatment: Pyophage (by enema), Fersis-phage (orally) in combination with enzymes, probiotics, microelements
Result: after 10 days - normal defecation, no sweating, intensity of hyperkinesia decreased
Clinical application

Case 2: Chronic infection

**Patient:** L.A., 86 years old, female (US), approached EPTC in 2015

**Diagnosis:** cystitis, infection in urinary tract, bacterial vaginitis, was diagnosed 45 years ago, last 15 years regular antibiotic-therapy

**Complaints:** Pain in small pelvis

**Bacteriological testing:** *E. coli* (10^8 pfu/ml)

**Susceptibility:** Pyophage, Intesti-phage

**Phage treatment:** Liquid phage application locally, per os for two weeks

**Result:** After 20 days of phage application – complete eradication of pathogen, No pain
Clinical application

Case 3: Chronic infection

**Patient:** J.O., Male 70 years old

**Diagnosis** - chronic gastroenterocolitis

**Complaints:** frequent diarrhea, bloating, abdominal pain in the lower half of epigastrium; diarrhea, with increased frequency of defecation (3-4 times per day)

**Clinical investigations:** confirmed gastritis, duodenitis, gastro and duodenogastral reflux and spastic colitis

**Bacteriological analysis:** *Klebsiella spp.* - 10⁷ cfu/ml (No commercial phage available). *E. coli*: 2x10⁸ pfu/ml (hemolytic - 20%)

**Susceptibility:** SES and ENKO phages, autophage for *Klebsiella* prepared

**Phage treatment:** *Per os* for two weeks in combination with probiotics

**Results:** Repeat analysis revealed: complete eradication of pathogens, recovery in the normal microflora; Patient's subjective condition dramatically improved - bowel movements were normalized, no pain or bloating
Clinical application

Case 4: Chronic infection

**Patient:** M.SH., male, 39 years old (Germany), approached EPTC in 2015

**Diagnosis:** Maxilla sinusitis

**Complaints:** pain on face and forehead, pus excreta from nose, was diagnosed in 2004, last 5 years regular antibiotic-therapy and pain-killers

**Bacteriological analysis:** *Streptococcus mitis, Enterococcus durans, Staphylococcus aureus*

**Susceptibility:** FERSIS phage, Intesti phage

**Phage treatment:** *Per os* and local wash-out by phages for two weeks

**Results:** Patient's subjective condition dramatically improved, drastic decrease of excreta, no need in painkillers
Clinical application

Case 5: Chronic infection

Patient: V.B., 48 years, female, (France), approached EPTC in 2016
Diagnosis: Systemic scleroderma, bacterial infection of low part of left leg (stump)
Bacteriological testing: *Staphylococcus aureus*
Susceptibility: SES phage, Staphylococcal phage

Phage treatment: Phage application locally in liquid and ointment for 20 days
Clinical application

Case 6: Chronic infection

Patient: E.G., female, 57 years old (Uruguay), (approached EPTC in 2015)

Diagnosis – Osteomyelitis (right leg); posttraumatic; subjected to several surgery, long antibiotic-therapy, deep wound infection

Complaints: bacterial infection of wound, infected metal piece, pus excreta

Bacteriological analysis of nose and oral cavity: *Staphylococcus aureus*, *Pseudomonas aeruginosa*

Susceptibility: Pyophage, Intesti phage

Phage treatment: Metal piece was removed after surgery, phages were applied locally during and after surgery, per os for two weeks

Results: Further development of osteomyelitis stopped, wound is free of infection, granulation, no need of amputation.

Next step: plastic surgery
Case 6

Before surgery

After surgery

Current picture of wound
Clinical application

Case 7: Post operational infection

Patient: F.B., 58 years, female (USA)
Diagnosis: Post operational wound infections, Pyodermia, Nasal furunculosis
Complaints: pain, swelling, redness around the wound and nostril
Bacteriological analyses: *S. aureus (MRSA), E. coli*
Susceptibility: Staphylococcal phage, Fersis phage

Phage treatment: Phage applications locally
Result: after 15 days – complete granulations and epitalization of chronic wounds
Why Phage Therapy?

• Serious problems of antibiotic-resistance
• Phage therapy – **ecologically safe approach** (do not affect normal microflora)
• No resistance with multi-component phage preparation
• There is **no correlation** between phage- and antibiotic-resistance
• 90 years of successful experience of using phages for therapy, prophylaxis and diagnostics in FSU
• **No serious side effects** have been reported from the Eliava Institute phages, despite use in **hundreds of thousands of people since it was introduced**
Why Phage Therapy?

• **Phages are available and easy to apply** (different forms: tablets, in liquid, suppositories etc.)

• **Compatible with the other therapy** (other antibacterial remedy, vaccine, probiotics)

• **Stable preparations** (no cold storage and long shelf life)

• **Cost effective** (in comparison to antibiotics)
Phage therapy gets revitalized

The rise of antibiotic resistance rekindles interest in a century-old virus treatment.

Sara Reardon

03 June 2014 | Corrected: 04 June 2014

Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria

The White House

Published on September 15, 2014 by gill

Today, President Obama signed an Executive Order directing key Federal departments and agencies to take action to combat the rise of antibiotic-resistant bacteria. The Administration also released its National Strategy on Combating Antibiotic-Resistant Bacteria. The President has also appointed a National Coordinating Council for Combating Antibiotic-Resistant Bacteria, which is charged with developing a comprehensive plan to reduce the use of antibiotics in food animals and promote the development of new antibiotics.
Challenges

• Virus!!!!!
• Lack of knowledge and understanding in Public
• No clinical trials performed according to the International standards
• Biological product – should be updated time by time
• Big pharma influence
THANK YOU

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