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New Case Reports with Phage Therapy-What is Needed for More?

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Case Report

A recent article had the provocative title: A wake-up call: we need phage therapy now [1]. Indeed, there are very few sources for phages available if someone needs them urgently. Thus phages are needed and should be produced, characterized and banked and provided upon need, possibly on a European basis. It is not so difficult to collect phages: wherever there are bacteria, there are also their phages. Thus, hospital sewage or general sewage are rich sources and then they require purification, characterization, typing of their hosts, banking and catalogues.

Promising History

Looking back into the history of phages will tell us some important information. A curing activity was detected in the river Ganges as the basis for rituals by Hindus, which was active against bacterial cultures. This activity was thermo-sensitive; it disappeared with heating of the river water, indicating some biological activity [2]. This was due to phages - before they were known, viruses of bacteria. Phages were applied to infectious epidemics since 1917 when Felix D`Herelle published his first paper against dysentery treated and cured with phages in the Institute Pasteur in Paris [3]. Interestingly, he isolated the phages from the stool of soldiers and used the filtrate on bacteria- which were indeed killed. We isolated phages from the feces of a human patient after feces transfer without knowing this history [4,5].

He traveled wherever some infectious diseases occurred and treated them with phages, South America, Africa (Ruanda, Burundi, Congo), passengers on a French ship in the Suez Canal, Mexico, Africa, India (Assam), and Russia! Felix D`Herelle even swallowed the phages to prove that they had no adverse effects [6]. He initiated the foundation of the Eliava Institute of Bacteriophages, Microbiology and Virology in Tsiblisi in Georgia in 1936. Phages are being produced there to this very day. Up to 1200 people were employed there at peak times and produced tons of phages. The military was a major recipient and driving force. Already in 1939 in the Finnish-Russian war 18.000 Soldiers received phage mixtures, "cocktails" against anthrax, dripped into their open fractures and 80% of them recovered without amputations [7]. To allow better shipment, phage powders were developed, also pills for front lines during World War II. In 1963 about 30.000 children were tested half of them receiving phage pills against Shigella bacteria and the other one placebos.

The number of children coming down with dysentery was reduced from 6.7 per 1000 to 1.8, thus 3.8 fold. They continued to use phage therapy because of the lack of antibiotics. In Tsilbisi also pills were designed and produced for easier transportation, up to 1.5 mio pills per year. Also Band-Aids were developed to cover wounds. Even prophylactic phage treatments were tested- however, that would require high bacterial doses, frequent application of the phages to allow their replication: It did not turn out useful unless during ongoing epidemics. Phages were even added to meals as prophylaxis. The results achieved in the Soviet Union and Tsiblisi throughout many decades will now have to undergo more stringent test conditions and scientific reporting. It is not well-known, that large cohorts including controls have been analyzed before, much beyond case reports, including controls, exact conditions, etc.

Three recent case reports are mentioned below

What are needed are controlled clinical trials to prove and specify the usefulness of a phage therapy against Multi Drug-Resistant (MDR) bacteria. We need to find out, whether phages can help against MDR bacterial infections and whether people can recover from untreatable infections by phage therapy. Pharmaceutical industry is not known to develop potential antibiotics, which could enter the market soon.

Three recent case reports

Some recent success stories with phage therapies against MDR bacteria in life-threatening diseases may be worth summarizing and evaluating. There is the patient Tom Patterson with an open-access public YouTube story. He got infected as a tourist in Egypt by a bacterium *Acinetobacter baumannii* and had health problems with pancreatitis and diabetes. His courageous wife S. Strathdee, an epidemiologist, activated doctors, agencies and colleagues in the US and finally succeeded in finding help for her husband by phage therapy. Out of 200 "natural" phages tested, finally three were applied. They were pretested in special animal systems, a wax worm model, whereby the wax worms are the caterpillars of the wax moth. One phage originated from a company AmpliPhi Corporation and the two others from a

military-linked Center for Phage Technology (CPT) in Texas. An emergency permission for an Investigational New Drug (eIND) from the Food and Drug Administration (FDA) allowed the application of three selected phage types by three consecutive intravenous injections. They immediately terminated a 3 months coma. Phage therapy was continued for up to 8 weeks and interestingly the phage effect increased when combined with antibiotics. The patient recovered [8]. Then a 15 year old girl with Cystic fibrosis received a lung transplant in England. A phage therapy was initiated against her MDR bacterial infection, *Mycobacterium abscessus*, which had destroyed her lung and still affected her skin and liver. (It is distinct form *Mycobacterium tuberculosis*, which is unfortunately very difficult to treat with phages due to its encapsidation.) She received three phage types specifically selected for her case, among them two engineered, i.e. Gene-Modified Organisms (GMOs).

A local sore on her chest was pretested since no animal studies were performed. She received 3 billion phages by intravenous injections every 12 hours for 32 weeks and phage therapy still continues up to now [9]. The third recent case was published in a Belgium newspaper, the "Saint-Luc baby", a 13 months old baby with liver and blood infections by MDR bacteria. She received phages for 85 days by a military doctor, Colonel Patrick Soentjens, from the Military Neder-over-Heembeck Hospital near Brussels. The phages were described as "trained" and "tailor-made" - whereby it is unclear, whether they were selected for or gene-modified. The production of the phages is worth mentioning because it was made by as "pharmaceutical compound" [10].

This is a routine production for crèmes or composite material directly prepared under well-defended conditions in a pharmacy, but normally not for biological such as phages. The Belgian Health authority, Sciensano, was involved. The World Health Organization has declared six MDR bacterial strains as most urgent targets for new therapies, described by the acronyme ESKAPE, indicating: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter*.

Conclusion from the recent case reports

Phages are not easily available and they need to be selected for to lyse the respective bacteria. There is no central banking or a phage library with pretested and readily available phages on demand for a therapy-which sometimes requires a rapid availability in the case of sepsis patients, who may die before phages can be selected and produced. Special phages may need to be selected for or even gene-modified ones have to be made in the laboratory in advance by recombinant technologies. Gene-modified bacteria have been recently described [11]. The new CRISPR/Cas9 gene editing technology allows fast genetic engineering [12]. But GMOs cannot easily be used under the rules of the European Medicines Agency (EMA). Time matters in urgent cases.

Furthermore, the therapy consisted in all cases in a mixture of more than one phage and it was even indicated, that they need to be compatible with each other. We know since the early days of Human Immunodeficiency Virus (HIV) therapies that triple therapies are required targeting diverse molecular mechanisms, to be successful to prevent resistance. Interestingly, some of the recent trials involved former HIV specialists. Apparently in the above-mentioned cases the infection was caused by one bacterium. This is not always the case; e.g. large burns are infected by a variety of bacteria. Using one phage against one target bacterium will not be successful as has been described in a study designated as PhagoBurn, which was supported by the European Union (EU) framework 7 [13]. If several MDR bacteria are involved, an average of three phages per bacterium may be required.

Furthermore the initial treatments as described above were applied intravenously. This is new and originally phages were preferentially envisaged for open wounds, fractures and deep sores such as gangrenes. Phage therapy has also been recently described successfully for diabetic toes of 11 patients who were not in life-danger but had to face amputations and were saved from surgery [14]. The phages only last for short periods, so that treatments had to be applied twice daily. The doses were high and required sufficiently high bacterial titers to be successful; otherwise the phages cannot multiply and die out. The numbers described are 10^8 plaque-forming units (pfu/ml) for phages and bacterial titers of 10^3 colony-forming units (cfu/ml).

We need new rules-and a new name

The requirements from legal European authorities such as EMEA for drugs refer to non-biological, products which are exactly defined, producible by highly standardized technologies and lots which are stored. Phages are biological and can vary if large amounts are produced. In the cases mentioned above the phages were made in small lots as needed. In the Belgium case the production was made by pharmaceutical compound magistral production, also named magisterial production. This was intensely advertised by the Belgium scientists JP Prinay and colleagues from the Queen Astrid Hospital in Brussels [15].

Yet legal authorities do not normally allow such productions. The "GMP" or "GMP-like" productions can fail with phages and their variability and are prohibitively expensive, amounting to millions of €. This was the case with the PhagoBurn study supported by the EU [13]. Thus, we need many groups who produce phages under identical conditions, purified and processed and then typed for their bacterial specificity. Sooner or later there will be GMO phages with broader host spectra. Such GMO-modified phages are presently not acceptable by agencies in larger clinical trails, except for individual compassionate trials, which normally do not have controls.

Also quite noticeable are the periods for therapies described above, the treatments had to be continued for very long times, for many weeks. It can be hoped that phages simultaneously applied with antibiotics prove faster success. Finally trials for testing one target and one therapeutic - is the rule for drug development. That is useless for phages, where more than one target and several phages per target will be the rule. We need new regulations for phages to find out, whether they will fulfill the high expectations:

Four legal "No-No's" need to be overcome:

- more than one target,
- multiple treatments for one target,
- no GMP but pharmaceutical production (compounding),
- Permission of GMO-phages.

Such trials may need to be redefined by n a new name!

Perhaps other countries can proceed with less stringent regulations. The technologies involved are simple and the phages are cheap. Felix D`Herelle produced phages in Brasilia, Russia, India and Canada, not only in Paris and Africa-we should remember that. Brasilia`s AIDS politics, even though breaking patent laws (not safety rules), was successful recently, which reduced the number of AIDS patients significantly. There are no patent laws for phages right now, thus the regulatory restrictions need to be overcome. Who will be the next country to try out this technology, if regulations delay the testing?

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