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## Phages in Treatment of Some Deep Skin Purulent Infections

**Introduction.** Resistant to the majority of antibiotics, bacteria in the last period became a big problem in medicine. Beside the intensive work of pharmaceutical industry we still have no new classes of antibiotics useful for treatment of many infectious diseases that is why the search of new ways and alternative means of treatment is so important for modern medicine. One of results of such search is the raised interest to the therapeutic possibilities of phages – the specific viruses which attack the bacteria and annihilate the pathogenic microorganisms. Phages were discovered by Felix d'Herelle in 1917 and already from 20-th years of XX-th century they have been widely used in the study of bacterial genetics and cellular control mechanisms as well as in an attempt to destroy bacteria. From this period started the efforts to use the phages in the treatment of intestinal infections [1, 6] and typhoid sepsis [3, 4], for infectious-allergic rinosinusopathy, infectious-allergic bronchial asthma and in the cases of suppurative inflammation process.

In the beginning of XX century phage therapy seemed to be very promising although it was a subject of much controversy. From the 40-th years its use in western countries was rather poor, but in Eastern Europe were performed serious clinical researches and their results confirm that phages really may play an important role in the fight with infections which resistance against the medical preparations is rising. Phages are thought to play a crucial role in the maintenance of diversity in natural bacterial communities. Theory suggests that phages impose density dependent regulation on bacterial populations, preventing competitive dominants from excluding less competitive species. Phages in dermatology were started to use for treatment of purulent diseases in the end of 30-th – beginning of 40-th years of the last century mainly as a topical treatment and it was described in a number of works [2, 4, 12]).

Such an approach was not high result able but in some cases of superficial bacterial flora it was effective. In one of the older studies, performed by Michael Beridze [2]

were described 143 cases of purulent skin infection caused by *Staphylococcus aureus*. All cases were divided in two groups - deep and superficial including such nosology as furunculosis, abscesses, hydroadenitis, impetigo and others. The methodology of treatment was thoroughly described and was used both possibilities – topical applications and injections. It was determined that the best results were received in the group of deep lesions with acute and sub-acute forms ranking highest, while the treatment of chronic forms was less efficient. There is rather a big list of other authors cited by Michael Beridze [2], who shared this conclusion and recommended that more individualized approaches to the treatment of specific cases might be more efficient but would create difficulties in the standardization of treatment schemes.

In 1957 were published the results of study provided by Vartapetov and presented by him a list of other authors studying clinical efficiency of bacteriophages in the treatment of purulent skin diseases. Based on received results Arcady Vartapetov [13] concluded that newly developed deep forms of dermatitis caused by Staphylococcal infection due to phage therapy are healed in a shorter period rather than the cases of the long-lasting and frequently repeated infections; in cases of newly developed infiltrates their rapid resolving occurs without degradation. If the degradation of the infiltrate still occurs due to phage therapy performed using Staphylo- or Pio- bacteriophage, the pus does not contain necrotic stem; phage therapy is less efficient in cases of hydroadenitis, if the abscess is already formed. In this case operation is required to release the pus prior to phage therapy supplied with penicillin treatment and self blood transfusions; positive results were observed in cases of phage therapy of abscesses among adults and especially young babies (with multiple abscesses); pains are usually released after 1-2 phage injections; inter-cutaneous injections of phages are more efficient than sub-cutaneous. This may be explained by the fact that in case of inter-cutaneous injections the phages are not so easily eliminated due to anatomical struc-

ture of the epidermis which is almost devoid of blood vessels; often a local reaction (redness, inflammation) may be observed in the sites of phage injection, which is not a counter-indication for further implementation phage treatment. Arcady Vartapetov mentions that all authors agree that healing in majority of cases occurs within 4-8 days, correspondingly the percent of the cured patients is in the range of 70.0-100.0 %.

As well authors [2, 8, 10, 11, 12, 13] attract attention to the immunobiological potential of the Staphylococcal bacteriophage. Currently in Georgia is observed a new wave of interest for phage therapy generally and in dermatology especially. The first report about treatment of skin purulent infections with phages was done in 2008 on the First Congress of Global Dermatology by Natalia Kiladze and Teona Shulaia [9]. It was a presentation of results of 5 years study of phagetherapy in different chronic suppurative skin diseases with approved prevalence of staphylococcal flora. The treatment was provided by produced by Giorgi Eliava Institute of bacteriophages, microbiology and virology, Tbilisi, Georgia. In all cases the prevalence of *Staphylococcus aureus* was proved by laboratory examination. For the treatment were used standard pyophages, produced by Giorgi Eliava Institute, which is a complex phage solution against *Staphylococcus aureus*, *Streptococcus* (different cultures), *Escherichia coli* (different serotypes), *Pseudomonas aeruginosa*, *Proteus vulgaris*, *mirabilis* and SES phages against *Staphylococcus aureus*, *Streptococcus* (different cultures), *Escherichia coli* (different serotypes).

**The purpose** of this communication, which is a continuation of previously presented research, is to report the data and results of treatment of such common chronic suppurative skin disease as chronic folliculitis of hairy area and uncommon chronic skin disease as perifolliculitis capitis abscedens et suffodiens with approved prevalence of staphylococcal flora by pyophages produced by Giorgi Eliava Institute, Tbilisi, Georgia.

**Materials and methods.** In the trial were included 87 patients aged 18 to 56, all males, among them with chronic folliculites - 52, with sycosis - 30, with folliculitis et perifolliculitis capitis abscedens et suffodiens, Hoffmann - 5. All patients still had active, recurring scalp lesions, no one of them had remission temporary and no one had concomitant acne vulgaris on the face. The exclusion criteria included: less than 2 months history of chronic scalp folliculitis; patients on immunosuppressant drugs like corticosteroids; immunosuppressant conditions like diabetes mellitus and malignancy. All of them were unsuccessfully treated before with antibiotics. Pus swabs from intact pustules were taken for culture and in all cases the prevalence of *Staphylococcus aureus* was proved by laboratory examination. Used for treatment pyophages, produced by Giorgi Eliava Institute, include *Staphylococcus aureus*, *Streptococcus* (different cultures), *Escherichia coli* (different serotypes), *Pseudomonas aeruginosa*, *Proteus vulgaris*, *mirabilis*.

Phages work best in direct contact with the infection and it was the reason that in the study for treatment was

used the mesotherapy technique. Mesotherapy technique was developed in France in 1958 by Dr. Michel Pistor. Today it is frequently used for medical pathologies and certain aesthetic conditions and has become a world standard for effective treatment of circulatory problems, alopecia, cellulite, ulcers and skin damage. Since the hair follicles and sebaceous glands are located in dermis and in any case of topical treatment we have to overcome the epidermal barrier with its different lipids that is practically impossible for solutions. Mesotherapy gives a possibility of administration of low doses of medicines through intradermal injections just into the target areas.

After disinfection of the skin with 0.5 mg/ml Chlorhexidine solution the phage solution was injected by dermal nappage, papula and point by point technique in all damaged areas. The technique of injections was depended on the elements of skin lesions. In the cases of folliculitis et perifolliculitis capitis abscedens et suffodiens Hoffmann intralesional injections were also done into buggy nodules and sinus tracts. The quantity of needed phages depended on the size of damaged areas. In each case the frequency of procedures were usually once in 3-4 days until healing. In such chronic cases of infection as folliculitis and sycosis mesophage therapy was prolonged sometimes up to 9-21 days. The most frequent side effects were: pain at the area of injections, itching, redness etc. The side effects were only temporary and usually followed by a rapid improvement within 12-24 hours. In all cases of sycosis patients were successfully treated during 20-25 days and did not need any additional procedures or topical treatment except disinfectants when shaving. Patients with folliculitis capitis needed more prolonged treatment with breaks, in these cases the injection were performed once in three days during 21 days, after a break for 7 days the course was repeated. Full recovery was achieved in all cases, but they were still under observation up to 2 months in order to avoid relapses. In 2 cases of chronic folliculites during the treatment there was also used topical isotretinoin which is available in Georgia. The prescription of this topical treatment in these two cases was connected with more deep and long-standing lesions with development of erythematous, fluctuant nodules. Use of topical isotretinoin was not prolonged – about 10 days and it was applied as an auxiliary mean.



In the cases of folliculitis et perifolliculitis capitis abscondens et suffodiens Hoffmann patients develop perifollicular pustules, nodules and abscesses, with interconnecting sinus tracts that drain pus or blood. Usually because of relapses and chronic trend the prognosis is poor. 3 of our 5 patients were treated before with oral isotretinoin which gave improvement, but relapses were still present. In one case few months ago treatment was provided with oral zinc sulfate, but unsuccessfully. In all these cases before treatment was done chemical peeling of hairy area with Jessner peel. The Jessner peel is generally considered a medium level peel containing 14.0 % of each acid (Salicylic, Lactic, and Resorcinol.) This combination will create a powerful reaction in the skin to help clear out pores and create a medium skin sloughing. Resorcinol as a part of the mixture is tanning and drying the skin and disinfecting it, salicylic acid produces a quick skinning of the epidermis and gives a bacteriostatic effect, and lactic acid exerts both exfoliating and anti-inflammatory effects, it also stimulates collagen and elastin production, and will soften the epidermis to allow for better penetration. The depth of this peel is determined by the number of layers applied during application and the tolerance level of the skin it is applied to. On the treated area were applied 2 coverings of the peeling mixture at intervals of 5 minutes.

After maintaining the interval - about 1 minute - the chemical composition was washed off. Peeling was used to remove the stratum corneum of the epidermis, pigment spots and smooth out small cicatricial changes and to facilitate access to underlying tissues. After successful finishing of exfoliation were done intralesional injections into bumpy nodules and sinus tracts and dermal nappage, papula and point by point technique in all damaged areas. Patients were treated within three weeks once in three days with following break of 7 days, after the course was repeated. In all 5 cases the final results were positive. The cosmetic defect in the form of a fibroid growth was still present, but after the course of treatment the laboratory data confirmed the absence of pathogenic flora in correlation with marked clinical improvement.



Before treatment



After treatment



Before treatment



After treatment

**Conclusions.** Phage therapy has a long history and phages potential for treating infectious diseases has been pursued since their discovery, but still there are many important questions that must be decided before their wide therapeutic use in different clinical fields. Their benefits are undeniable, this therapy may replace or augment the conventional antibiotic therapy, help eliminate antibiotic resistance of bacterial strains and they give a real chance for patients suffering from chronic infections caused by antibiotic-resistant bacteria.

There is a need to develop phage therapy of purulent skin diseases, but more research is needed to understand bacteria-bacteriophage interactions in the skin community to obtain comprehensive knowledge on different pathogenic flora.

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Стаття надійшла до редакції журналу 29 травня 2017 р.

## Phages in Treatment of Some Deep Skin Purulent Infections

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**Introduction.** The questions of treatment of chronic skin purulent infections are extremely important due to their wide spread, severe clinical course of some nosological forms, development of resistance to the traditional means, and growth of undesirable side effects of antibiotic therapy. Chronic suppurative skin diseases connected with skin appendages are disorders of common occurrence and a major constituent of pyodermas. They still remain a problem due to their chronic character and difficulty of treatment, as well as its large impact on patients' quality of life. Due to the chronic course of the disease, treatment is long lasting, and often ineffective because of resistance to antibiotics therefore it is desirable to provide the treatment with effective alternatives to commonly used antibiotics to reduce the resistance and obtain a highly specific agent which is able to destroy bacteria effectively. In the same time across the world a growing number of scientists are noting the promising positive results of phage therapy and its advantages, especially in the treatment of chronic cases.

The **aim** of this communication, which is a continuation of previously presented research, is to report the data and results of treatment of some common chronic suppurative skin disease with phages.

**Materials and methods.** In the present investigation were included 87 males aged 18 to 56 with chronic folliculites ( $n=52$ ), syccosis ( $n=30$ ) and folliculitis et perifolliculitis capitis abscondens et suffodiens, Hoffmann ( $n=5$ ), in all cases was approved prevalence of staphylococcal flora and all of them were treated before with antibiotics, but unsuccessfully. The treatment was provided with pyophages produced by Giorgi Eliava Institute (Tbilisi, Georgia) which include *Staphylococcus aureus*, *Streptococcus* (different cultures), *Escherichia coli* (different serotypes), *Pseudomonas aeruginosa*, *Proteus vulgaris*, *mirabilis*.

Taking into consideration deep locations for treatment was chosen mesotherapy technique - phage solution was injected by dermal nappage, papula and point by point technique in all damaged areas. In each case the frequency of procedures was usually once in 3-4 days until healing, the process took about one month. In patients with folliculitis full recovery was achieved in all cases, but they were still under observation up to 2 months in order to avoid relapses. In the cases of folliculitis et perifolliculitis capitis abscondens et suffodiens Hoffmann treatment was started with M. Jessner's peeling followed by intralesional injections into buggy nodules and sinus tracts and dermal nappage, papula and point by point technique in all damaged areas. Patients were treated within three weeks once in three days with following break of 7 days, after the course was repeated. In all 5 cases the final results were positive. The cosmetic defect in the form of a fibroid growth was still present, but after the course of treatment the laboratory data confirmed the absence of pathogenic flora in correlation with marked clinical improvement.

**Conclusions.** Phage therapy has a long history and phages potential for treating infectious diseases has been pursued since their discovery, but still there are many important questions that must be decided before their wide

therapeutic use in different clinical fields. Their benefits are undeniable, this therapy may replace or augment the conventional antibiotic therapy, help eliminate antibiotic resistance of bacterial strains and they give a real chance for patients suffering from chronic infections caused by antibiotic-resistant bacteria. The experience in phage therapy may become very important with the rapidly-increasing spread of antibiotic-resistance bacterial infections which are difficult to treat now.

There is a need to develop phage therapy of purulent skin diseases, but more research is needed to understand the bacteria-bacteriophage interactions in the skin community to obtain comprehensive knowledge on different pathogenic flora.

**Keywords:** pyobacteriophages, folliculitis, mesotherapy.

## Фаги в лікуванні деяких глибоких гнійних захворювань шкіри

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**Вступ.** Хронічні гнійні захворювання шкіри, що пов'язані з її придатками, виникають часто і є складовою піодермії. Через хронічний перебіг і труднощі лікування вони значною мірою впливають на якість життя пацієнтів, оскільки в разі резистентності до антибіотиків лікування стає малоефективним.

**Мета.** Подати звіт про результати лікування таких гнійних захворювань як хронічний фолікуліт волосистої частини голови та абсцедивний підривний перифолікуліт голови підтвердженої стафілококової етіології піофагами виробництва інституту імені Гіоргі Еліава (Тбілісі, Грузія).

**Матеріали й методи.** У дослідження включено 87 чоловіків віком 18–56 років із хронічним фолікулітом ( $n = 52$ ), сикозом ( $n = 30$ ) і абсцедивним підривним фолікулітом та перифолікулітом Е. Гоффмана ( $n = 5$ ) із бактеріоскопічно підтвердженим переважанням стафілококової флори.

Для лікування використані піобактеріофаги виробництва інституту «Бактеріофаг» імені Гіоргі Еліава (Тбілісі, Грузія). Беручи до уваги глибину уражень, застосували метод мезотерапії – ін'єкції піофагів за допомогою дермального напaju, папульно й точковим методом у всі ушкоджені ділянки. Процедури проводили раз на 3–4 дні до повного загоєння, лікування тривало близько місяця.

**Результати.** У хворих із фолікулітом у всіх випадках досягнуто повного одужання. З метою спостереження за станом пацієнтів вони перебували під наглядом упродовж двох місяців. У випадках абсцедивного підривного фолікуліту та перифолікуліту Е. Гоффмана першим етапом лікування був пілінг М. Джесснера, а далі інтрадермальні ін'єкції в гнійні вузли й пазухи та дермальний напaj, папульне й точкове введення у всі ушкоджені ділянки. Курс лікування: три тижні раз на три дні з наступною перервою на 7 днів. Після цього курс повторювали. У всіх п'яти випадках остаточні результати були позитивними, і, незважаючи на те що косметичний дефект залишався, бактеріоскопічне дослідження підтверджувало відсутність бактеріальної флори.

**Висновки.** Переваги лікування гнійних захворювань шкіри голови фагами є беззаперечними, адже їх застосування може підсилити або ж замінити традиційну антибіотикотерапію. Із огляду на це, існує потреба у подальшому вивченні проблеми.

**Ключові слова:** піобактеріофаги, фолікуліти, мезотерапія.