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BACTERIOPHAGES AGAINST METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* STRAINS

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Abstract. Bacteriophages against methicillin resistant Staphylococcus aureus strains. Poniatovskyi V.A., Bondarchuk O.L., Prystupiuk M.O., Smikodub O.O., Shyrobokov V.P. *Staphylococcus aureus is one of the most common opportunistic pathogens that causes a variety of diseases, from minor skin infections to life-threatening sepsis, meningitis, pneumonia and a number of other diseases. Particular attention was paid to methicillin-resistant Staphylococcus aureus (MRSA) strains with multiple drug resistance. The purpose of this study is investigation of the sensitivity of clinical isolates of Staphylococcus aureus, including methicillin-resistant strains, to bacteriophage drugs and determination of possibility of using this agent for the treatment of staphylococcal infections. A number of classical and modern microbiological methods for the isolation and identification of Staphylococcus aureus: an indication of genes, responsible for antibiotic resistance (PCR analysis), determination of sensitivity to antibiotics (disc diffusion method) and bacteriophages (spot test, Gracia method, Appelman method) were used in the study. The susceptibility analysis of Staphylococcus aureus with presence and absence of mecA gene to the commercial bacteriophage product – "PYOFAG® BACTERIOPHAGE POLYVALENT" was performed. The results of the study showed that the total number of susceptible strains of bacteria was 95±0,2%. The use of investigational Bacteriophage drug for the treatment of furunculosis caused by MRSA has shown positive results. After one week of using the bacteriophage as monotherapy, the patient experienced regression of the clinical symptoms. For the period of use no adverse effects have been detected. Thus, the phage drugs using can become an important tool in the control of antibiotic-resistant strains, which cause a variety of infections in humans.*

Реферат. Бактеріофаги проти метицилін-резистентних штамів Staphylococcus aureus. Понятовський В.А., Бондарчук О.Л., Приступюк М.О., Смікодуб О.О., Широбоков В.П. *Staphylococcus aureus є одним із найпоширеніших опортуністичних патогенів, що здатні викликати різноманітні захворювання: від незначних шкірних інфекцій до небезпечного для життя сепсису, менінгіту, пневмонії та ряду інших захворювань. Особлива увага приділяється метицилін-резистентним штамам Staphylococcus aureus (MRSA) зі стійкістю до багатьох лікарських засобів. Метою цього дослідження є вивчення чутливості клінічних ізолятів золотистого стафілокока, у тому числі метицилін-резистентних штамів, до бактеріофагового препарату та встановлення можливості використання цього засобу для лікування стафілококових інфекцій. У роботі використано ряд класичних і сучасних мікробіологічних методів виділення та ідентифікації мікроорганізмів,*

проведено визначення генів, що відповідальні за антибіотикорезистентність (ПЛР-аналіз), здійснено визначення чутливості ізольованих культур до антибіотиків (диско-дифузійний метод) та бактеріофагів (Spot-тест, метод Граціа та метод Аппельмана). Проведений аналіз чутливості збудників гнійно-запальних захворювань (Staphylococcus aureus), з наявним та відсутнім геном mecA, до препарату на основі бактеріофагів. Чутливість визначали до комерційного препарату – «Піофаг® бактеріофаг полівалентний». За результатами дослідження було встановлено, що загальна кількість чутливих штамів бактерій до препарату становила 95±0,2%. Використання комерційного препарату для лікування фурункульозу, викликаного MRSA, також дало позитивний результат. Вже за тиждень застосування бактеріофагового препарату в пацієнта відбулася регресія клінічної симптоматики. За період використання фагового засобу побічних ефектів не виявлено. Отже, застосування бактеріофагових препаратів може стати важливим інструментом у боротьбі зі стійкими до антибіотиків штамами, що викликають різні інфекції в людини.

Infections caused by antibiotic-resistant microorganisms are a significant threat to the modern health system. The number of such poly- and multiresistant strains is steadily increasing.

One of the most common pathogens of healthcare associated or nosocomial infections is methicillin-resistant strains of *Staphylococcus aureus* (MRSA). These are important opportunistic microorganisms and are included in the ESKAPE group of pathogens [13]. The spread of MRSA significantly contributes to increased morbidity and mortality rate among patients staying in clinical departments with different nosological forms, prolonging the time of their hospitalization and increasing economic burden. According to the data of Alessandro Cassini et al., the specific gravity of MRSA among isolates of *Staphylococcus aureus* in the EU countries varies considerably from 26.6% (2007) to 16.8% (2015) [6]. According to the data collected by research scientists, in Ukraine, in all bacterial carriers the number of methicillin-resistant strains among coagulase-negative staphylococci (MR-CNS) was 42.8%, which almost doubled the prevalence of coagulase-positive staphylococci (MR-CPS) – 16.6% [4].

In the process of evolution, microorganisms have developed various mechanisms of resistance to antibiotics. The history of the study of antibiotic resistance began with the discovery of penicillinase in *Staphylococcus aureus* – the first of a series of β-lactamases; non-sensitivity to methicillin correlates with resistance to other β-lactam antibiotics. The development of resistance is associated with low affinity of β-lactams with penicillin-binding protein 2a, the synthesis of which is the responsibility of the mecA gene. This gene is present only in methicillin-resistant strains. Reduced sensitivity to oxacillin is also possible due to hyperproduction of β-lactamases. *Staphylococcus aureus* strains with reduced sensitivity to oxacillin are called BORSA (border line oxacillin resistant *S.aureus*), and the described modification of penicillin-binding proteins is called MODSA (mechanism of methicillin resistance in *S. aureus*). Both variants can be addressed as "false" MRSA, since they lack the mecA gene. To validate this statement, it is necessary to determine the genetic characteristics of each individual strain [2].

In order to investigate the prevalence and detection of new outbreaks of MRSA-related diseases, it is necessary to apply the latest molecular genetic methods that can provide adequate information about genetic features and differences between individual isolates. Most common analytical methods used for this purpose are: pulsed-field gel electrophoresis (PFGE), multilocus sequencing-typing (MLST), spa-typing (sequencing of the staphylococcal protein A gene site, which includes the tandem arrays, of the so-called X region), SCCmec typing, and genome-wide sequencing [15].

In consideration of the aforementioned, the fundamental task of modern science is the development of new antibacterial agents that would highly selectively act on the bacterial targets in both acute and chronic infections. One of the natural ways to overcome the problem of antibiotic resistance is the use of bacteriophages. Due to the strict specificity of the action of phages, unlike antibiotics, phages do not attack the body's resident flora, do not have toxicity, do not cause allergic reactions at the infection site of target bacteria. The activity of the phage is not affected by antibiotic resistance in bacteria.

Today, phage therapy of infectious diseases is becoming a popular and effective tool against pathogenic microorganisms. Research is being conducted to obtain modified bacteriophages using genetic engineering. Rebekah M. Dedrick et al. first used engineering phages to treat a patient with a disseminated antibiotic-resistant variant of mycobacterial infection caused by *Mycobacterium abscessus*. Intravenous use of the phage was well tolerated and associated with objective clinical improvement, including closure of the chest wound, improved liver function and significant disappearance of infected skin nodules [9].

Bacteriophage drugs can be used both as monotherapy and in combination with antibiotics. There is an increasing number of reports on the improvement in efficacy of antibiotic therapy after

introduction of bacteriophages into the treatment protocol. Sanjay Chhibber et al. used linezolid in combination with bacteriophages for the treatment of diabetic foot. This combination was much more effective against infection compared to monotherapy. The entire tissue healing (remodeling) was also accelerated. This approach can serve as an effective strategy in treating infections caused by MRSA [7]. It has also been shown an increase in the efficacy of antibiotics in relation to biofilms of *Staphylococcus aureus* in vitro after adding phages. Dickey J. et al. found that most antibiotics were ineffective at low concentrations in relation to biofilms, but the addition of phages to treatment regimens led to a significant improvement in their efficacy [8].

MATERIALS AND METHODS OF RESEARCH

Research was conducted at Kyiv City Clinical Hospital No. 4, Department of Surgery No. 2 and Department of Microbiology, Virology and Immunology of Bogomolets National Medical University.

Isolation and identification of microorganisms: The strains of *Staphylococcus aureus* isolated from biological material with various infectious pathologies (phlegmons, boils, abscesses, bacterial carriers, etc.) were used for the research. The material was collected in compliance with the aseptic regulations using sterile disposable cotton swabs. The material was collected prior to the start of antibiotic therapy and the use of local antibacterial agents and bacteriophages. Immediately after collection, the swab was immersed in a universal transport medium and delivered to the laboratory. Inoculation was carried out by semi-quantitative method on solid and liquid nutrient media. For bacteriological studies, several different nutrient media were used: agar with 5% blood content, yolk-salt agar with mannitol (Chistovich's medium), Endo medium, sterility control media and sugar broth. Inoculation of the studied material was carried out using the "swab-loop" method. The inoculated material was incubated in the thermostat for 18-24 hours at 37°C. Inoculation was examined on the first day, and all species of microorganisms grown on solid nutrient media were counted. The culture properties were noted. Subsequently, based on a combination of biochemical properties (according to Bergey classification), the pathogens of the species were identified [3].

Determination of sensitivity to antibiotics was performed using a conventional disk diffusion method; the study was conducted in accordance with the Order of the Ministry of Health of Ukraine No. 167 dated 05.04.2007 "On Approval of the Guidelines "Determination of Sensitivity of Microorganisms to Antibacterial Drugs" [5]. The following antibiotics were used for the test: amoxicillin, oxacillin, cefalexin, cefotaxime, ceftriaxone, cefepime, ciprofloxacin, levofloxacin, clarithromycin, azithromycin, vancomycin, amoxiclav, chloramphenicol, linezolid and doxycycline.

PCR diagnostics: To differentiate "true" from "pseudo" methicillin resistant strains of staphylococcus aureus, a commercial test system produced by "DNA technology Ltd." was used to carry out PCR reaction. The studies were conducted in accordance with the manufacturer's guidelines. The test system involves defining the mecA gene both in the culture of *Staphylococcus aureus* and directly in the biological material [2].

Phage preparation: The bacteriophage drug “PYOFAG® BACTERIOPHAGE POLYVALENT” (Marketing Authorization Holder NeoProbioCare Inc., Canada), was subjected to the study.

Determination of the sensitivity of isolated strains to bacteriophages: 18-24-hour broth cultures were used to study the sensitivity to phages. The preliminary conclusion on phagosensitivity was made on the basis of a spot test. Confirmation of sensitivity was carried out using two classical methods: in the liquid nutrient medium – the Appelman method, and in the dense medium – the Gracia method [1].

Statistical analyses were performed using t-test, by licensed software IBM SPSS Statistics Base v.22.

RESULTS AND DISCUSSIONS

The obtained experimental data on specific activity of bacteriophage preparations on clinical isolates of *Staphylococcus aureus* indicate that the studied drug has a pronounced specific lytic effect in relation to the strains used (Table 1). 95±0.2% of clinical isolates of staphylococci were found to be sensitive to the action of the studied bacteriophage (19 out of 20). All three strains that were resistant to most antibiotics and had the mecA gene according to data of PCR diagnostics were sensitive to the action of “PYOFAG® BACTERIOPHAGE POLYVALENT” (Fig. 1).

At the second stage, the bacteriophage drug “PYOFAG® BACTERIOPHAGE POLYVALENT” was used for the treatment of infectious pathology of staphylococcal etiology in patients of the surgical department of the Kyiv City Clinical Hospital No. 4.

Patient P., born in 1968, applied for medical assistance. Upon examination by a surgeon, multiple furuncles were found throughout the body. Based on the clinical picture, the results of laboratory diagnostics and the patient’s complaints, a diagnosis was established – generalized furunculosis. Concomitant disease: plaque psoriasis, progressive stage; psoriatic arthropathy.

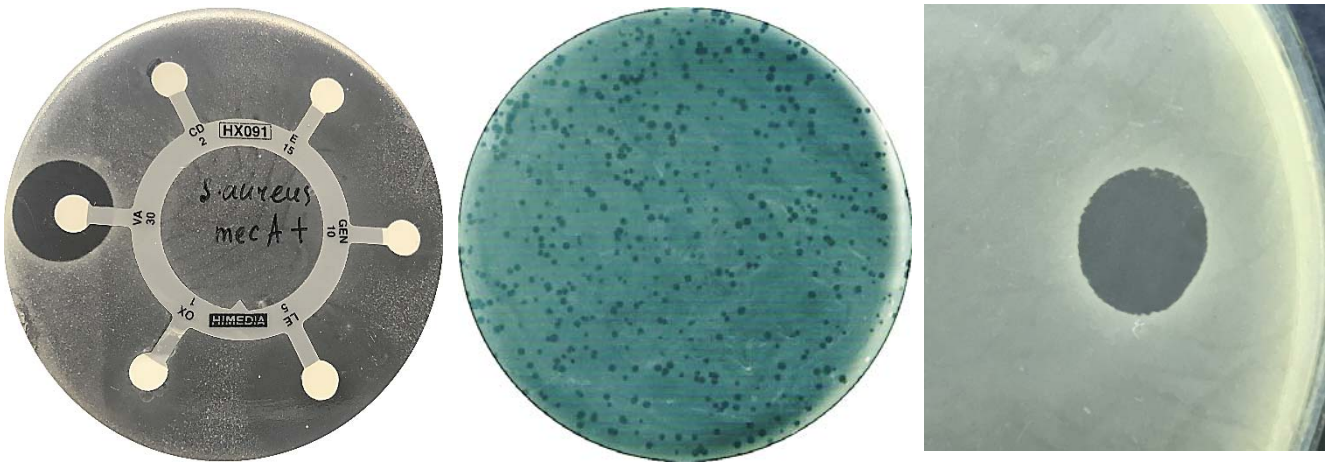
Table 1

Sensitivity of different strains of *Staphylococcus aureus* to the drug "PYOFAG® BACTERIOPHAGE POLYVALENT"

Strains	*Staphylococcus aureus (p≤0.01)*	
	MSSA (n=17)	MRSA (n=3)
Number of strains	17/16*	3/3*
Total	20/19*	

Note. * Total number of strains/sensitive to bacteriophage

When collecting anamnesis, it became known that the patient has been a carrier of *Staphylococcus aureus* for a long time, which was confirmed by the results of previous bacteriological examinations (constant secretion of *Staphylococcus aureus* from the nose and tonsils). Periodically, furuncles were formed on various locations on the body. In the anamnesis there is also a deterioration of patient's state after surgical treatment of the first furuncles under unfavorable conditions (a medical institution with unsatisfactory sanitary conditions in one of the tropical countries). Patient passed courses of antibiotic therapy and surgical treatment (opening of boils). Treatment with antibiotics (according to generally accepted protocols), even those that showed sensitivity in an *in vitro* study, led to the selection and preservation of more resistant pathogen populations, and, consequently, multiple resistance and constant reduction of remission periods.



a. *b.* *c.*

Fig. 1. Specific activity of bacteriophages and antibiotics in relation to *Staphylococcus aureus* with the mecA gene: a. – sensitivity to antibiotics by disc diffusion method; b. – sensitivity to bacteriophages by appelman's technique; c. – sensitivity to bacteriophages by spot test

A bacteriological analysis of the secretions from the furuncles was carried out: in the biological sample a significant amount of gram-positive cocci was found, which showed a pronounced growth on yolk-salt agar with mannitol in the form of golden, smooth colonies, lecetovitelase activity was absent. On blood agar, the growth was defined as white, smooth colonies with β-hemolytic activity. The use of the disk diffusion method demonstrated the resistance of the isolated strain to a significant number of antibiotics used (Table 2). According to general recommendations, confirmation of resistance to oxacillin, detected by one of the routine methods, is a prerequisite for assigning the strain MRSA status. One of the generally accepted standards for confirmation of MRSA is genotype analysis of the strain for the presence of the mecA gene. The corresponding test systems, developed for this purpose, are becoming valuable tools in the work of clinical laboratories. Our research of the isolated strain by PCR method revealed the presence of the mecA gene, indicating true methicillin resistance.

The patient was offered a bacteriophage preparation for the treatment of furunculosis – topically

and per os, with "PYOFAG® BACTERIOPHAGE POLYVALENT". At the end of phagotherapy, the clinical picture significantly improved.

Two months later, the patient repeatedly sought for medical assistance due to recurrence of furunculosis. During the bacteriological examination, a strain of *Staphylococcus aureus* from the nasal cavity was also isolated separately.

Furthermore, the *S.aureus* strain, was typical in culture characteristics and had lecithovitelase activity.

Table 2

Sensitivity to antibiotics of separated isolates

Indexes	Sensitivity		
	strains from furuncles		20.03.2019 (strain from nose)
	07.11.2018	02.04.2019	
mecA gene	+	-	-
PYOFAG®	**sensitive**	**sensitive**	**sensitive**
Amoxicillin	**resistant**	**resistant**	**resistant**
Amoxiclav	**resistant**	**resistant**	**resistant**
Oxacillin	**resistant**	**resistant**	**low sensitive**
Vancomycin	**sensitive**	**sensitive**	**sensitive**
Clindamycin	**sensitive**	**sensitive**	**sensitive**
Cefotaxim	**sensitive**	**sensitive**	**sensitive**
Ceftazidime	**resistant**	**sensitive**	**sensitive**
Ceftriaxon	**sensitive**	**sensitive**	**sensitive**
Cefoperazone	**low sensitive**	**sensitive**	**sensitive**
Cefepim	**sensitive**	**sensitive**	**sensitive**
Cefalexin	**sensitive**	**sensitive**	**sensitive**
Ciprofloxacin	**resistant**	**resistant**	**resistant**
Levofloxacin	**resistant**	**resistant**	**resistant**
Clarithromycin	**resistant**	**resistant**	**resistant**
Doxycycline	**sensitive**	**sensitive**	**sensitive**
Linezolidium	**sensitive**	**sensitive**	**sensitive**
Azithromycin	**resistant**	**resistant**	**resistant**
Lincomycin	**low sensitive**	-	-
Meropenem	**sensitive**	**sensitive**	-
Co-trimoxazole	**sensitive**	-	-

Isolated microorganisms differed in sensitivity to antibiotics and absence of the mecA gene (PCR data) from those previously isolated from the furuncles. The results of the sensitivity of isolated strains of *Staphylococcus aureus* to 21 antimicrobial drugs from different groups, which have the greatest practical importance in the treatment and sanitation of carriers, are shown in Table 2. The difference in the properties of strains isolated from different loci and at different times suggests that the strains that caused the recurrence of furunculosis are exogenous in origin.

The patient received repeated treatment, which included the use of only "PYOFAG® BACTERIOPHAGE POLYVALENT" without the use of antibiotics. The bacteriophage was used locally, as well as introduced into the oral and nasal cavity for the disinfection of possible foci and prevention of endogenous spread of the pathogen. In addition, an antiseptic was used for surface treatment around the furuncles (Fig. 2).

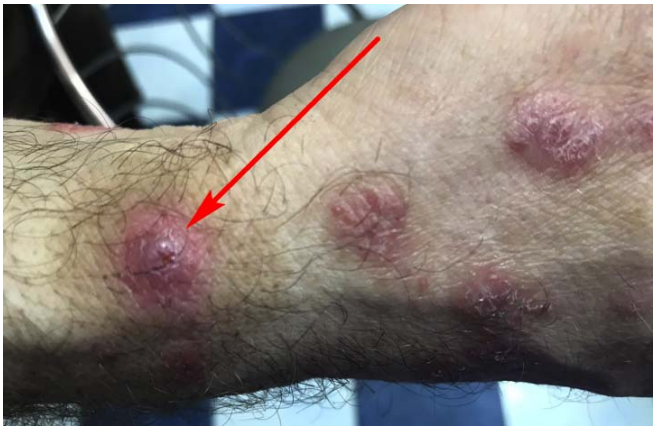


Fig. 2a.

Before treatment with bacteriophage medicinal product. Presence of furuncles

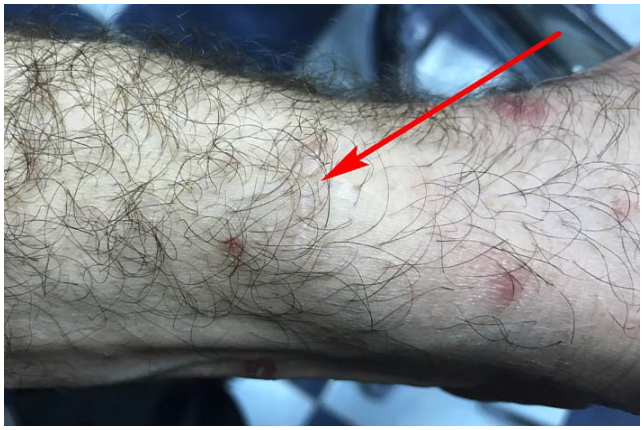


Fig. 2b.

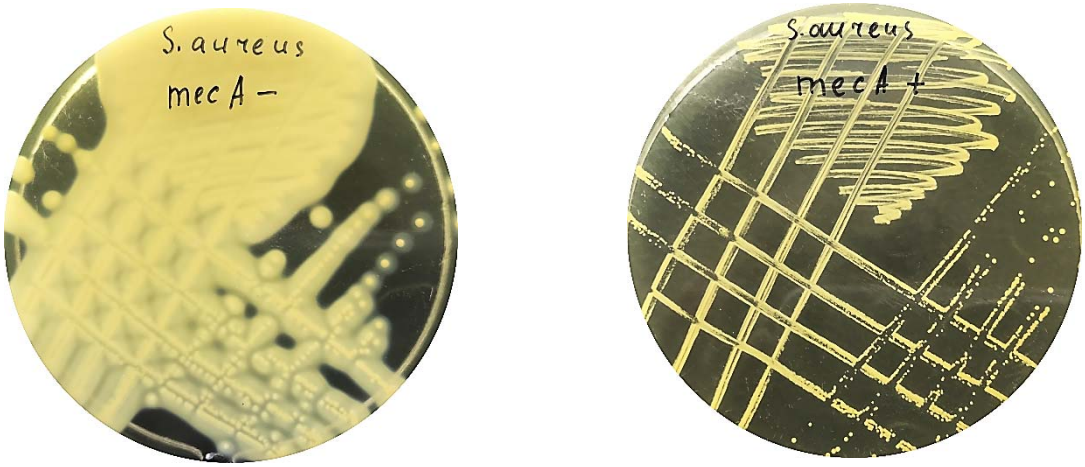
14th day of treatment with bacteriophage medicinal product. Disappearance of furuncles and scarring of tissues after the use of bacteriophage medicinal product

The efficacy of the treatment was evaluated by patient's subjective perception and clinical picture of the disease. After a week of repeated use of bacteriophage medicinal product, the patient experienced regression of clinical symptoms. Repeated bacteriological examination of the nasal and oral cavity for the presence of strains of *Staphylococcus aureus* were negative. During the use of bacteriophage, no adverse events were reported.

Many authors have established the efficacy of phages in vitro in relation to MRSA, including biofilm forms [8, 11], as well as in vivo on laboratory animals [10]. Medical efficacy in the fight against methicillin-resistant *Staphylococcus aureus* using bacteriophages has also been demonstrated by other researchers [7]. Leszczyński P. et al., using treatment with phage products, managed to eliminate the bacterial carrier and cure urinary tract infection caused by the methicillin-resistant *Staphylococcus aureus* [14].

Ryszard Międzybrodzki, along with the medical efficacy, demonstrated economic value of using bacteriophages. Reducing the cost of treatment of antibiotic-resistant infections with the use of phages is an important additional argument for the wider use of bacteriophage-based formulations in medical practice [12].

One of the features of the clinical isolates of *Staphylococcus aureus* with the presence of the mecA gene was the absence of lecithinase activity (Fig. 3). This property is very important from a practical point of view, since one of the diagnostic markers that allows differentiating *S.aureus* from *S. epidermidis* and is usually used in clinical laboratories is the presence of lecithovitelase activity. Thus, it may lead to misclassification of *Staphylococcus aureus* with the mecA gene to the group of epidermal staphylococci and, therefore, to underestimation of the prevalence of *Staphylococcus aureus* in the human population and correct determination of the etiological factor of an infectious disease.



a. *b.*

Fig. 3. Growth of *Staphylococcus aureus* on yolk-salt agar with mannitol: a. – in the absence of the mecA gene; b. – in the presence of the mecA gene

CONCLUSIONS

1. The using of bacteriophages can become an important tool in the fight against antibiotic-resistant strains that cause infectious pathology in humans.

2. The using of bacteriophages as monotherapy is an effective and safe way to treat bacterial infections.

Conflict of interests. The authors declare no conflict of interest.

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