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Review Article

Phage Therapy as a New Approach in Treating Emerging Antibiotic Resistant Infections

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HIGHLIGHTS

- Bacteriophage can be used as an antimicrobial agent for treatment of bacterial infection.
- Bacterial resistance to routine antibiotics is a big challenge in the world.
- Specificity toward bacteria is one of the important characteristic of phages.

ABSTRACT

Despite the progress in treatment of infectious diseases, ability of microorganisms to develop the resistance to routine antibiotics has still remained as a big global challenge in clinics. This subject matter keeps the infections top in the list of life threatening diseases especially in those individuals suffering from nosocomial infections. The importance of this global health challenge urges researchers to find an alternative solution with more efficacies to treat infections. There are some alternative approaches by which the global spread of resistant bacteria could be controlled. Through these ways, using bacteriophages instead of different generation of antibiotics brings many promises. According to results of different studies using bacteriophages in the management of infectious disease especially in nosocomial infections not only helps to reduce the spread of antibiotics resistance but also raises the hopes for the rescue of the suffering patients. Bacteriophages can open a new therapeutic window in the control and the treatment of the infectious disease with better efficacy.

Introduction

Our knowledge about the mechanisms which microbes use to evade novel antibiotic agents and inactivating new antibiotics is crucial, as we are now facing substantial infectious-disease challenges (Havaei et al., 2010; Ghasemi et al., 2013). The history of antibiotics discovery and antibiotics resistance show this fact that while, we try to use high potent and newly board spectrum antibiotics to control infections, microbes evolve new strategies to evade. The emerging of resistant strains of bacteria is more threatening when exists among hospitalized patients. The current stage of nosocomial infections and their mortality rates indicate to this fact that there is an essential need for new approaches to combat emerging infections and the global spread of drug-resistant bacterial pathogens (Pourmand et al., 2012; Liapikou et al., 2013).

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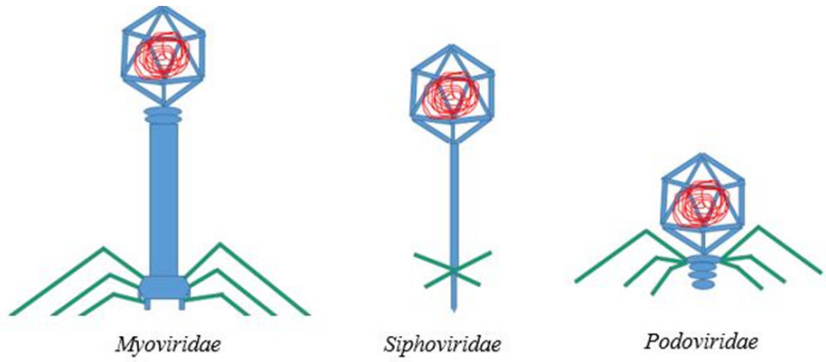

Figure 1. Schematic presentation of the caudovirales families.

Bacteriophage therapy

Phage therapy including the therapeutic use of bacteriophages is considered as one of the new approaches for treating infection especially with resistant bacteria. Historically, application of bacteriophages returns to the ancient time when reports of river waters with ability to cure infectious diseases, such as leprosy, have been documented. In fact, bacteriophages are bacterial specific viruses that act much more specifically than antibiotics (Kingwell et al., 2015).

Synthetic chemotherapeutics agent (salvarsin and sulpha drugs) were the first antibacterial compounds that were discovered by human. Surprisingly, phage therapy was the second option before antibiotics. The first antibiotic (penicillin) has been tested in 1930 after two decades of the first phage therapy in 1919 (Wainwright et al., 1986). Discovery of antibiotics causes the phage therapy to be superseded for a long time, but nowadays by the presence of MDR (multi-drug resistant) bacteria, a need for new alternative or combination therapy urges scientists to reconsider phages and their potential for eradicating infectious bacteria (McCarville et al., 2016).

The narrow spectrum and specificity allow bacteriophages to be chosen as harmless agents not only to the host organism (human, animal, or plant), but also to other beneficial bacteria such as gut flora (Chapot-Chartier, 2014). In this regard, using bacteriophages for the treatment of infections can reduce the risk of opportunistic infections due to keeping the good bacteria. As bacteriophages only replicate in vivo, a much smaller dose is needed to have therapeutic effect, this is another advantage of phage therapy instead of antibiotic therapy. Bacteriophages also tend to be more successful than antibiotics especially in case of biofilm covered bacteria such as *Pseudomonas aeruginosa* or *Staphylococcus aureus*, to which antibiotics typically cannot penetrate to (Chhibber et al., 2013). Interest in bacteriophages has recently renewed worldwide, and the laboratory tests suggest that bacteriophage-based therapy may be beneficial for the treatment of pulmonary infections in cystic fibrosis (CF) patients (Hraiech et al., 2015). Meanwhile, as antibiotic resistance has become a major health problem against very current and important pathogen like *Staphylococcus* or *Mycobacterium*, currently bacteriophages are considered as a good candidate to replace (or in combination with antibiotic therapy) antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) (Kali et al., 2013; Jensen et al., 2015). Of note, the application of bacteriophages is not limited to infections, they can also serve as drug-delivery platform to kill cancer cells (Bar et al., 2008). Generally, there are two strategies of phage therapy to eradicate unwanted bacteria, to use natural phages or engineered phages (synthetic-based).

Natural phage therapies

Recent phage therapy as a novel antimicrobial infection is focused on the use of lytic tailed phages. The lytic tailed phages are member of *Caudovirales* order, whose families are *Myoviridae*, *Podoviridae*, and *Siphoviridae* (Fig. 1) (Wittebole et al., 2014).

The *Caudovirales* are an order of viruses known as tailed bacteriophages and used in natural phage therapy (non-recombinant). *Caudovirales* have double stranded DNA (dsDNA) genomes, and a tail appendage that is attached to the icosahedral head of phage with a connector protein (Ackermann et al., 2012).

One of the advantages of tailed bacteriophages is that they can be found easily everywhere that bacteria are living (in animal, plants, etc.) (Hatfull et al., 2011). When tailed phages infect bacteria, before lysing the bacteria membrane to release its progeny virions, it

Table 1. Synthetic phages based on T7 phage and T3 phage.*

Synthetic phage	Structure	Characteristics
T7T3 (C-gp17)	combination of T7 phage with 410 aa of the C-terminal of T3 tail fiber	it can form plaque on *E. coli* ECOR16
T7T3 (gp17)	combination of T7 phage with whole T3 tail fiber	it can form plaque on *E. coli* ECOR16
T3T7 (C-gp17)	combination of T3 phage with the 405 aa of the C-terminal of T7 tail fiber	it can form plaque on *E. coli* BW25113 and *E. coli* MG1655 (like T3T7(gp17))
T3T7 (gp17)	combination of T3 phage with whole T7 tail fiber	it can form plaque on *E. coli* BW25113 and *E. coli* MG1655 (like T3T7(C-gp17)
T713a (C-gp17)	combination of a synthetic T7 phages (with optimized codon) with C-terminal amino acids of the phage 13a tail fiber	it can form plaque on *E. coli* efficiently (but T7 and T7WT cannot)
T713a (gp17)	combination of a synthetic T7 phages (with optimized codon) with whole amino acids of the phage 13a tail fiber	it can form plaque on *E. coli* so efficiently (but T7 and T7WT cannot)
T3R (gp17)	combination of synthetic T3 phage with the R tail fiber	it can infect *E. coli* BL21, *Klebsiella* sp. 390 and Y. *ptb* IP2666
T7K11 (gp11-12-17)	combination of T7 phage with K11 phage tail	it can infect *Klebsiella* sp. 390 but not *E. coli*
K11T7 (gp11-12-17)	combination of K11 with T7 phage tail	it can infect *E. coli,* but not *Klebsiella*

* Based on information of reference (Ando et al., 2015).

exploits many cellular systems of bacteria for production of virions and killing bacterial host (Chevallereau et al., 2016). Specificity toward bacteria is one of the important characteristics of phages. Some phages can infect a few strains through one species and some of them can infect many strains through different species; for example some polyvalent phages like *Mu* that can infect many species like *Escherichia*, *Erwinia*, *Citrobacter*, *Enterobacter,* and *Shigella* (Ross et al., 2016). Also polyvalent *w812* phage can infect around 700 strains of *Staphylococcus aureus* and lyses them (Pantůcek et al., 1998). This characteristic of phages can help to eradicate just the specific unwanted bacteria within many available bacteria through the body, which cannot be done by Antibiotics, especially broad-spectrum ones. Many antibiotic treatment side effects like diarrhea is because of dysbiosis effect and overgrowth of MDR strain of microorganisms which are all because of non-selective effect of chemical antibiotics (Francino et al., 2016). So the specificity and accuracy of phages activity can help to maintain the eubiosis and health of gastrointestinal microenvironment (Sulakvelidze et al., 2001; Sarker and Brüssow, 2016). Broader host range phages are selected in process of screening and isolation; it means that the phages are isolated from environment and then screened against the commonly occurring bacteria causing diseases for determining the host rang of phages. One of the limitations of phage therapy is narrow host range of some phages which can be solved by using a phage mixture (phage cocktail). This cocktail can trigger many different host and receptors to prevent resistant mutant bacteria (Yen et al., 2017).

Synthetic phage therapies

By innovation of DNA sequencing technology and advancement of genetic engineering methods, it became possible to engineer and design recombinant phages with appropriate and novel characteristics. For example to broaden the bacterial host ranges of phage, it is possible to hybrid tails of some related phages (Table 1). Also by recombinant technology some genetic properties can be added to phages, for example by addition of specific gene sequence for expressing exopolysaccharide-degrading enzyme, necessary for targeting biofilm, it is possible to improve the diffusion of phages (Lu and Collins, 2007; Lin et al., 2012). Also it is possible to engineer p genes to express some cell-penetrating peptides to help phages break the mammalian membrane (Staquicini et al., 2011; Rangel et al., 2012). One drawback with natural phage therapy is that natural phages kill bacteria through lysing and rupturing bacterial cell (Roach and Donovan, 2015). Subsequent to fast lysis, the endotoxin of bacteria will release and cause inflammation in surrounding environment. To overcome this problem some engineered phages are designed in a way that they are knocked out in cell lysing genes (endolysin); so they

are bacteriostatic instead of being bactericidal and also, they are called temperate phages (Matsuda et al., 2005; Nemeth et al., 2015). Engineered bacteriostatic phages also may be used as an adjuvant in antibiotic therapy to deliver some genes helping in disruption of bacterial cell-to-cell communication in biofilm which can improve antibiotics penetration (Pei and Lamas-Samanamud, 2014) or to design some temperate phages that carry sensitizing cassette genes and deliver these sensitizing proteins into the bacteria and thus sensitize bacteria to antibiotics (Edgar et al., 2012). But always there is a risk of benefit of prophage encoded genes for bacterial as a host (Cumby et al., 2012). Also nonlytic bacterial death can be induced by the use of phagemid (phages that contain a plasmid within the phage origin of replication) that carry genes of some toxin protein and some peptide with antibacterial properties (Krom et al., 2015) and also making some sequence-specific CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system in phagemids to sensitize bacterial population toward antibiotics and killing bacteria indirectly (Bikard et al., 2014; Citorik et al.,2014; Pires et al., 2016). Antibiotic-resistant genes can be eliminated by phagemid that carry CRISPR RNAs sequence and subsequently disrupt transferring resistant genes to other bacterial strain, and as bacteria have not efficient end-repairing systems, double stranded break induced with CRISPR cannot be repaired and will cause bacterial death (Bikard et al., 2014; Cui and Bikard, 2016).

Phage therapy

The use of bacteriophage as an antimicrobial therapy known as phage therapy, have been tested in acute and chronic infectious diseases. But mostly the focus of recent phage therapy has been done on acute infection of small vertebrate animal. In some studies, phage therapy reduces the amount of bacteria to a level that host immune system could be able to fight and remove the bacterial infection (Smith and Huggins, 1982; Debarbieux et al., 2010; Alemayehu et al., 2012). Many phage therapy studies have been done in treatment of pulmonary infection with antibiotic resistant phenotype like in pneumonia cystic fibrosis patients (Will et al., 2005; McVay et al., 2007; Chhibber and Kumari, 2008; Debarbieux et al., 2010; Singla et al., 2015) and patient suffering from gastrointestinal infections (Sarker et al., 2016).

Phage therapy in chronic infection

Chronic infections may be caused by persistent (years or even decades) uncured infection which will show resistance to current antibiotics therapy. Chronic infections that might be made up from a population of diverse bacterial strains, create poly-microbial biofilms making a strong barrier for penetration of antibacterial agents. Even though specific antibody against chronic bacterial strain antigens may be detectable in serum, this is not enough to eradicate infections (Malik et al., 2017).

In the study of Alemayehu et al. (2012) they used two bacteriophages (*myovirus* (ϕNH-4) and a *podovirus* (ϕMR299-2) that can kill both mucoid (NH57388A) and non-mucoid (*P. aeruginosa* MR299) *P. aeruginosa* strain when forming biofilm on cystic fibrosis epithelial cell lines (CFBE41o). After transfection of the epithelial cell line with the phages, the titer of phages increased 100 fold which demonstrates that phages are replicating in bacteria. Also this phage mix was tested on murine lung contaminated with *P. aeruginosa* which effectively reduces the number of bacteria 3-4 fold log unit in 6 h.

Gutiérrez et al. demonstrated that the 24 h biofilm of *S. aureus* IPLA16-rifR and *S. epidermidis* LO5081 was exposed with phages *phiIPLA-RODI* and *phiIPLA-C1C* while this phage therapy caused 5 log reduction of bacteria concentration with lytic ability of phages and also caused reduction of 2 log bacteria adherence of biofilms Gutiérrez et al. (2015). In another study by D.R. Alves et al. (2014), six novel bacteriophages that can effectively kill *P. aeruginosa* PAO1, were clinically isolated by screening process. This phage cocktail was tested on two types of static and dynamic 24 h biofilm models (which have been prepared under static and dynamic conditions). The cocktail effect (after 4 h contamination) on static biofilm model caused 95% eradication of biofilm biomass, but the effect of cocktail on flow biofilm model was a little slower and the dispersion of biofilm and 4 log elimination of cells occurred after 48 h contamination.

Phage therapy in acute infection

Phage therapy has been tested on many types of acute diseases but in this review it is point to some of the most common one.

Phage therapy of antibiotic resistance respiratory infections

Phage therapy is a new approach of treatment of respiratory infection caused by bacteria, such as *Burkholderia cepacia* complex (BCC), *Staphylococcus aureus*, *Haemophilus influenzae*, *Mycobacterium Tuberculosis* (TB), *P. aeruginosain,* Cystic fibrosis (CF) patients, and also Ventilator-associated-pneumonia (VAP) occur by *P. aeruginosa*, *S. aureus*, *Streptococcus* pneumonia, *H. influenza*, *Acinetobacter baumannii*, *Klebsiella* sp., *Enterobacter* sp., and *Serrati* sp. (Semler et al., 2014; Bodier-Montagutelli et al., 2017; Trend et al., 2017).

Phage therapy of antibiotic resistance wounds

Treatment of chronic wound like burning and diabetic

wound is a big worldwide problem. Bacteria that form biofilms are current in wound infection and reduced metabolic activity in biofilm and biofilm barrier for penetration of antimicrobial agents (antibiotics and antiseptics) make the treatment problematic. Two bacteria are important in resistant wound infections; *S. aureus* and *P. aeruginosa*.

In one study by McVay et al. (2007) thermal burned mice were infected with lethal *Pseudomonas aeruginosa* and then were treated with single dose administration of cocktail phage (consist of three different *P. aeruginosa* specific phages) in three different routes of intramuscular (IM), subcutaneous (SC), or intraperitoneal (IP). The study showed that phage therapy increased survival rates to 22-87% (8% without treatment) and also the treatment result was route dependent; the best result (87% survival) was seen in IP route of administration. Pharmacokinetic study of phage therapy showed IP administration resulted in earlier detected and higher concentration of phages in the blood, spleen, and liver (McVay et al., 2007) in comparison to IM or SC routes. The better result of IP route (earlier delivery of phages, longer remaining in circulation, higher concentration, and earlier detection of phages in many host organs) of administration of phages has been shown in one other study too (Chhibber et al., 2008). In another study by Chhibber et al. (2013), BALB/c mice with diabetic food *S. aureus* infection were evaluated by administration of phage MR-10, linezolid antibiotic, and non-treated control groups. The results showed that the group treated with both phage MR-10 and linezolid showed the higher reduction of bacterial load in wound in comparison to other treatment groups.

Phage therapy of antibiotic resistance gastrointestinal infections

In a study by Yen et al. (2017), three-phage ICP cocktail (against *V. cholerae*) administered to two animal models of *cholera* pathogenesis (mice and rabbits). The ICP phage cocktail orally administered to infant rabbit and mice 24 h before *Vibrio cholera* infection as prophylaxis. This phage cocktail reduce the colonization of *V. cholera* in infant mice and prevent the onset of the symptom of cholera in infant mice and this cocktail was effective as a prophylaxis treatment.

Tanji et al. (2005) performed a study to evaluate a cocktail of three phages SP15, SP21, and SP22 which were selected from feces of animal and sewage. These three phages were tested against batch cultures of *E. coli* and they saw the reduction in turbidity of the cell culture. They suspend phage cocktail in $CaCO_3$ buffer for oral administration to the mice that were infected with *E. coli* O157:H7 cells 2 days before. For 9 days after treatment the feces of the mice were assessed for presence of phages and bacterial cells. More rapid reduction in bacterial number and higher concentration of phages in mice feces and gastrointestinal tract were seen in group which received daily and repeated oral administration of cocktail phages. However, after day 9 of test period, the concentration of bacteria in feces of mice divided into two groups: group 1, who were treated with phages and group 2, who were not treated after infection with bacteria (control group) were not much different.

Stanford et al. (2010) tested the effect of a polymer-encapsulated phages (Ephage) that is a cocktail phage which consist four wV8, rV5, wV7, and wV11 bacteriophages that target *E. coli* O157:H7.They knew that these bacteriophages that targeted *E. coli* O157:H7 are sensitive to low pH and they will lose their activity in 20 min in acidic condition of gastric milieu. So, the Polymer encapsulated form of this cocktail phage whose recovery percent activity after exposure to low acidity situation was acceptable (13.6%) rather than non-encapsulated one were tested on 16 steers. 24 steers were infected with nalidixic acid-resistant *E. coli* O157:H7 (10(11) CFU) on day 0. 8 steers out of 24 were kept as control group without any treatment. The other was treated with Ephage on days -1, 3, 6, and 8, in two ways. Eight steers were treated with Ephage that was put into gelatin capsules (each capsule contain $10^{(10)}$ PFU) and the other 8 steers received the Ephage that were top-dressed on their feed ($10^{(11)}$ PFU per steer). Shedding of bacteria were tested for 10 days by fecal and swap sample. Both treatment strategy activities were acceptable and it was a little more in gelatin capsule way ($1.82 \times 10^{(9)}$ PFU/g in gelatin capsule and $1.13 \times 10^{(9)}$ PFU/g by food). Surprisingly phages treatment did not decrease the concentration of bacteria in fecal but it reduced the duration of shedding of bacteria for 14 days in both way of treatment in comparison to control group.

In one study by Bardina et al. (2012), a cocktail phage compromise of three bacteriophages (UAB_Phi20, UAB_Phi78, and UAB_Phi87) against *Salmonella enterica* serovar *Enteritidis* and *Typhimurium* in two animal models was tested. In mouse model, one dose of the cocktail was administered exactly at the same time of infecting mouse by Salmonella and booster doses in 6, 24, and 30 h after infection induction. Mouse survival was 50% after phage therapy. In White Leghorn chicken specific-pathogen-free (SPF) model the best result (reduction of Salmonella concentration in cecum) was seen in one phage therapy exactly one day before bacterial infection and colonization of bacteria in intestinal and again in days after infection.

Phage therapy trial in human

The most information on human phage therapy comes from two Eastern Europe countries, in the Poland in Hirszfeld Institute of Immunology and Experimental Therapy in Wrocław, the largest city of Poland and in Georgia especially in Eliava Institute of Bacteriophages,

Microbiology and Virology. The Eliava Institute mainly works on producing phage cocktail formulation and implementation (Gill et al., 2010). Georgia is the first country in the world that used bacteriophages in medical practice as a standard route for both treatment and prophylaxis. A number of medical product and also over the counter phage therapy formulation are available for many applications in self-remediation or physician administered in non-serious problem. Many clinical trials have been done in Georgia so far, but much incomplete and no more information is available from those. Hirszfeld Institute in Poland is the second important source of information on phage therapy. They mainly work on individual therapy with phages in patient who suffer from antibiotic resistance and many studies and papers re available with details (Kutter1 et al., 2010).

In this section some studies done on human have been pointed. In study by Bruttin and Brüssow (2010), the safety of bacteriophage on 15 healthy adults volunteer was assessed. Some volunteers received *E. coli* phage T4 with high dose (10^5 PFU/ml), some received lower phage T4 dose (10^3 PFU/ml) in their drinking water, and some volunteer just received placebo. In the group that received higher dose of phage T4, phages can be detected in their fecal after one day of exposure but this prevalence was half in volunteers who received lower dose phage. Oral administration of phages did not decrease the *E. coli* number in fecal sample of volunteers. No critical adverse effect was recorded in this study (just five people complained about gastric problems like nausea, more peristalsis movement, and stomachache and also just one complained about sore throat but none of them required any treatment). This adverse effect was not related to phage dose. No T4-specific antibodies were detected in serum and the serum transaminase level was in normal range after treatment (Kutter et al., 2010).

Rhoads et al. (2009) have done a phase I trial to test the bacteriophages for wound that are difficult to treat. It was tested on 42 patients with chronic venous leg ulcers (VLUs) but just 32 of them continue up to the end of the trial. The duration of treatment was 12 weeks and they were divided into two groups; test group, that were treated with bacteriophage cocktail compromised of specific phages against *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *E. coli* and the control group, that were treated with normal saline washing of wound. The result of 24 weeks follow up showed that there was no significant difference between the control and test group in terms of adverse effect, safety, and in rates of wound healing and also the efficacy should be studied in phase II trial.

Wright et al. (2009) developed a double blind small Phase I/II clinical trial on 24 patients with chronic otitis related to antibiotic resistant *Pseudomonas aeruginosa*. The patients were divided into two groups of treatment with phage and received placebo. Twelve patients were administered 0.2 ml (10^5 PFU/ml) of a cocktail of six bacteriophages (named as Biophage-PA) dissolved in 10% glycerol in phosphate-buffer saline, in their infected ear by dropping the phages by a needle. All patients visited 3 times after medication on days 7, 21, and 42 and were assessed by ear swap sample for *P. aeruginosa* strain resistant to antibiotics. Neither local and systemic toxicity nor any other important side effects were reported. In contrast to control group, the count of *P. aeruginosa* in treated group was dramatically lower and the treatment was safe and had an appropriate efficacy.

Sarker et al. (2016) recently studied a T4-like coliphages and placebo in children (6–24 month old males) with acute bacterial diarrhea by oral administration for 4 days. No adverse effect and also no improvement in child diarrhea situation were not recorded. The scientists of this study claimed that the treatment failure was possibly because of low titer of *E. coli* in gut transit of children (as coliphages, or any bacteriophages, need high titer of bacteria for amplification to be effective) and also coliphage was orally administered to children without any anti-acid for protection from low acidity situation of stomach.

Another trial has been done recently by Fish et al. (2016) on 6 human with diabetic toe infections (bone and soft tissue infection by *Staphylococcus aureus* including most methicillin- resistant *Staphylococcus aureus* (MRSA) strains) that did not show desirable response to current antibiotic treatment. In this study weekly wound care was done as soft tissue debridement and dropping single lytic phage Sb-1 with broad host range against *S. aureus* (that is commercially available in Tbilisi, Georgia by Eliava Biopreparation in 10 ml vial containing around 10^7–10^8 PFU/ ml) into wound cavity and then wrapped the wound for 48 h with gauze. This staph mono-phage topical treatment was successful in all patients. All patients' wound healed in around 6 weeks of bacteriophage therapy and just one special case (extremely poor vascularity) needed more treatment up to 18 weeks for wound healing (Sarker et al., 2016).

Rose et al. (2014) worked on a cocktail phage consist of tree bacteriophages against *Pseudomonas aeruginosa* and *Staphylococcus aureus* (named BFC-1 bacteriophage cocktail), which contain 10^9 pfu/ml of each phage) colonized on burn wounds. This trial was done under the approval of Belgian Medical Ethical Committee. Nine patients with burn wound infection received this cocktail phage 10 times. Half of patients received required systemic antibiotic treatment and the other half received BFC-1 as treatment (1 ml BCF-1 per 50 cm^2 of burned area). Bacterial load was not changed in biopsy result of wound after treatment (both groups, treated with phage and antibiotic). However, they claimed that may be this result was because of low bacterial load in wound before the treatment. Also, Rose et al. understood that this was

better to spray the phage cocktail into the wound and also suggested formulating phage cocktail as gel or as a wound part of dressing.

Conclusion

Although, despite of all above benefits of using bacteriophages for the treatment of bacterial infections, it should be noted here that the strain specificity may be counted as a disadvantage and limiting factor for this promising agents (Pérez Pulido et al., 2016). In fact a phage will only kill a bacterium in which there is a specific ligand for attachment. To overcome this problem and to improve the chances of success, the mixtures of phages as "bacteriophage cocktail" is often applied. The Recombinant phages and non-replicating phages derived from the conventional phages by genetic manipulation also dragged attentions due to their much more host diversity (Yuan et al., 2013). Genetically manipulated phages especially those encode lysosomal enzymes can be used as an adjuvant along with antibiotics for the treatment of hard to cure infections (Qadir et al., 2015). Bacteriophages in the management of infectious disease especially in the category of nosocomial infections, not only help to reduce the spread of antibiotics resistance but also, raised the hopes for the rescue of suffering patients (Abedon et al., 2011).

This is also important that it is possible for bacteria to develop resistance against phages, but in comparison to antibiotic resistance, the phage resistance might be easier to overcome (Labrie et al., 2010). Although the natural hosts for bacteriophages are bacteria, the patients' immune system in some cases can also mount an immune response to the phage and this may be considered as another drawback of phage therapy (Górski et al., 2012).

Taken together, regarding to the global spread of bacterial resistant strains like MRSA and the importance of limiting antibiotic administration against this type of bacteria, the application of phages can at least have benefits for reducing the multidrug resistant strain, but still more studies are needed to introduce this strategy as totally safe. Also for entering the clinics, the phages need to pass more clinical trials.

Competing Interests

The authors declare no conflict of interest.

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