



The Potential of Phage Therapy in Sepsis

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Sepsis remains a difficult clinical challenge, since our understanding of its immunopathology is incomplete and no efficacious treatment currently exists. Its earlier stage results from an uncontrolled inflammatory response to bacteria while in the later stage disturbed immune response with immunodeficiency syndrome develops. More than a hundred of clinical trials have not provided an efficient therapy which could ascertain an improvement or cure. Recent advancements in immunobiology of bacterial viruses (phages) indicate that in addition to their well-known antibacterial action phages have potent immunomodulating properties. Those data along with preliminary observations in experimental animals and the clinic strongly suggest that clinical trials on the efficacy of phages in sepsis are urgently needed.

Keywords: phages, sepsis, immunomodulation, immunodeficiency, application of phages

Sepsis is the leading cause of death in critically ill patients. More than 30 million cases of sepsis occur worldwide each year, and it is increasing 9–13% annually with a mortality rate of approximately 33% (1). Sepsis is considered to be an uncontrolled inflammatory response to bacterial infection associated with immunosuppression, an inability to clear infection and predisposition to nosocomial infections. Excessive release of oxidants and proteases by neutrophils is responsible for associated organ injury, especially in the lungs, as intrapulmonary sequestration of neutrophils and acute respiratory distress syndrome are its frequent complications (2), while the abdomen and urinary tract are also often affected (1). Also, exacerbated release of inflammatory cytokines and the resulting hyperactivation of immune cells (“cytokine storm”) appears to be important contributing factors. Although no single mediator or pathogen is responsible for the pathophysiology of sepsis, bacterial toxins (especially endotoxins) play a pivotal role in this disorder. In the past 25 years, the definitions of sepsis and septic shock and concepts of their pathophysiology have been hotly debated, with no gold standard achieved (3). Given the complexity of sepsis pathophysiology and its non-specificity with regard to infection, more than a hundred clinical trials have been carried out targeting the host response to infection, yet none of them has yielded a reliable treatment modality assuring clear clinical efficacy (1). Therefore, the development of new treatment modalities to prevent the progression of initial stages of sepsis to multiorgan failure and death is urgently needed (4). Host-directed therapy (HDT) is an emerging concept in anti-infective therapy meant to counteract the action of host factors required by pathogens for replication and persistence, to stimulate protective immunity, and to achieve a balance of immune reactivity to pathogens. Its major strategy is to upregulate the activity of phagocytes and limit inflammation (5). This strategy is supported by observations indicating that neutrophils may play a beneficial and deleterious role in the outcome of sepsis (6).

In the past decade, our understanding of bacteriophages (phages) and their current and potential position in microbiology and immunobiology has undergone major changes and has gained a new dimension. The original concept of phage highlighted its well-known antibacterial action, and the

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resulting practical therapeutic implications included the use of phage in antimicrobial therapy—especially in antibiotic-resistant infections. Given the increasing crisis of antimicrobial resistance, the interest in phage therapy has increased tremendously as more data suggesting its safety and efficacy have accumulated. Nevertheless, data showing the ability of phages to interact with the immune system and to modify its functions strongly suggest that phages may cause immunomodulating effects which can have practical implications for therapy. Of particular interest are the following immunomodulating activities of phages:

- (1) Phages show strong anti-inflammatory properties that may be independent of their well-known antibacterial activities. The possible mechanisms responsible for this effect may involve LPS binding, inhibition of excessive reactive oxygen species production and induction of IL-10 production. It has been shown that phages and their proteins may diminish inflammatory infiltration induced by endotoxin and allogeneic transplantation, and lower clinical indices of inflammation in patients on phage therapy (CRP, sedimentation rate, leukocytosis). In fact, a decrease of CRP in some patients may be very significant even though eradication of infections has not been achieved (7, 8).
- (2) Phages do not activate murine and human dendritic cells and may inhibit skin allograft rejection in normal and presensitized mice as well as dampen autoimmune reaction in a mouse model of collagen-induced arthritis (9, 10). They induce the anti-inflammatory IL-1 receptor antagonist (IL-1RA) synthesis by human mononuclear cells, a cytokine blocking the expression of pro-inflammatory cytokines and inhibiting the activation of Th1 cells and macrophages (11). Interestingly, IL-1RA blockade was associated with significant improvement in survival of patients with sepsis (12). Recent data confirm that the administration of recombinant IL-1RA can be beneficial in septic patients in whom its adequate levels have been achieved (13). Phages may also downregulate the expression of TLR4 (whose activation induces secretion of pro-inflammatory cytokines) (11). Interestingly, it was recently demonstrated that in a model of post-septic mice TLR4 deficiency improves immune paralysis; therefore, modulation of TLR4 activity may be useful in treating sepsis (14). Phages may also interact with platelets (PLT), which may be viewed as “the underappreciated orchestrator of the immune system” (15). PLT may participate in the leukocyte recruitment leading to increased severity of inflammation and their aggregation in this condition in response to agonist is amplified (15). Phages inhibit platelet (PLT) adhesion to fibrinogen and cause some reduction of T cell adhesion to that protein. In addition, thrombin-induced PLT aggregation *in vitro* may be decreased (9). PLT role in host response to sepsis has been subject of intense research (16) and more studies are needed to determine if indeed phage interactions with PLT may contribute to beneficial effects in sepsis.

Phage therapy may lead to downregulation of excessive immune responses, thus contributing to maintenance of

immune homeostasis. This mode of action may depend on the initial immune status of an individual causing upregulation when the immune response is depressed and downregulation when it is hyperactive: for example, abnormal B cell function returned to normal values in patients on phage therapy (7). Furthermore, phage therapy-dependent upregulation of cytokine production when it was initially low and lowering in patients in whom it was initially high was also noted (17). Recent reviews have described immunomodulating activities of phages in detail (7, 9, 18).

- (3) In almost 50% of patients on phage therapy, an increase in phagocytosis was noted which was associated with good clinical outcome. This observation seems to be a strong argument for phage treatment of sepsis: as noted, stimulation of phagocytosis is recommended as an important part of anti-sepsis strategy (5). Phages do not induce granulocyte degranulation, an effect which could contribute to further tissue injury (19). When confronted with bacteria phages facilitate microbial phagocytosis by human granulocytes (20). In this regard, it should be noted that the discoverer of phages, d’Herelle, determined that phages act as specific opsonins markedly facilitating bacterial phagocytosis (21).

Our data strongly suggest that phage therapy does not impair human granulocyte and monocyte ability to kill invading and standard strain bacteria and may even correct monocyte deficiency in patients with urinary tract infections treated with phages (22). The observed amelioration of phagocytosis reflects the outcome of a variety of factors influencing phagocyte functions in patients on phage therapy, one of the most important being pathogen burden. It is well known that pathogens have developed countermeasures to avoid detection, thereby impairing signaling and paralyzing machinery underlying phagocytosis and that neutrophil functions are depressed in patients with chronic infections. This deficiency may result from pathogen activity and therapy (e.g., antibiotics) (23, 24). Other authors have shown that neutrophils are required to control both phage-sensitive and phage-resistant pathogens; importantly, phages alone were unable to clear bacterial infection in neutrophil-depleted mice. Thus, the success of phage therapy depends on synergistic activities of phagocytes and phages, a phenomenon referred to as “immunophage synergy” (25). In accord with this assumption, reducing pathogen burden by phages may contribute to alleviating pathogen-dependent impairment of phagocyte functions. Evidently, those activities of phages in combination with their antibacterial functions strongly suggest that they could be of value in the treatment of sepsis. In particular, early phage administration could help eradicate infection, limit inflammation, and upregulate phagocytosis (which are the key recommendations of the HDT and may prevent the development of full-blown sepsis with resulting organ failure and death) (5). Recent data indicate that phages may induce IL-10 production by human mononuclear cells (11). IL-10 has been recognized as a potent anti-inflammatory cytokine limiting cell and tissue injury during bacterial infections. In a rat model of sepsis-induced acute kidney injury, upregulating IL-10

expression by macrophages was associated with attenuation of sepsis (26). In a positive feedback loop, IL-10 may also induce this cytokine in neutrophils, both *in vitro* and *in vivo* (27). Using a whole blood assay simulating the *in vivo* situation it was shown that IL-10 downregulates neutrophil phagocytosis of bacteria (28) confirming earlier data (29). On the other hand, IL-10 may upregulate phagocytosis in monocytes (28, 30). Therefore, IL-10 may have opposing effect on different phagocyte populations. Excessive secretion of IL-10 may contribute to immunosuppression typical for later stages of sepsis (31). Therefore, phage treatment of later stages of the syndrome may be more problematic when ensuing immunosuppression prevails. However—as

pointed out previously—phages have been demonstrated to upregulate *in vivo* and *in vitro* cytokine production in patients with immunodeficiency; moreover, available data suggest that phage therapy is safe also in animals and patients with various forms of immunodeficiency syndrome (19). **Table 1** shows the possible influence of phages on immune response during early and advanced stage of sepsis.

Interestingly, the potential application of phages (and their enzymes, lysins) in the treatment of sepsis has already received some experimental support, both in experimental animals and the clinic. **Table 2** presents the reported data on phage/lysins efficacy in the treatment of sepsis caused by different pathogens (32–49). In addition, there are initial clinical observations supporting the experimental data. We have reported good results in sepsis patients when phages were administered orally (50). Phages can translocate from the gastrointestinal tract; in addition, this route of administration was also found to be efficient in the mouse model (34).

In 2017, two cases of successful phage treatment of sepsis were reported. A patient with peritonitis, severe abdominal sepsis and renal insufficiency received phage against his *Pseudomonas aeruginosa* isolate intravenously. Immediately, blood cultures turned negative, CRP dropped and fever disappeared, and renal function recovered. Recently, a dramatic result was reported in a patient with sepsis in the course of necrotizing pancreatitis caused by *Acinetobacter baumannii*. Administration of phages intravenously and percutaneously into abscess cavities caused

TABLE 1 | Phage-induced immunomodulation at the early and advanced stage of sepsis.

Sepsis	
Early stage	Advanced stage
↑ Production of IL-10	↑ Immunomodulation
↓ ROS production	↓ ROS production
↓ Inflammatory infiltration	↓ Inflammatory infiltration
↑ Phagocytosis	↑ Phagocytosis
↑ Intracellular killing	↑ Intracellular killing
↑ LPS-binding	Lack of granulocyte degranulation

↑, increase; ↓, decrease.

Phage therapy may induce various types of immunomodulation in consecutive stages of sepsis.

TABLE 2 | Bacteriophages and phage lysins in the treatment of sepsis.

Antibacterial agent bacteriophage (B) or lysin (L)	Animal model	Pathogen	Route/time of phage/lysins administration (bold font—the best protection)	Reference
B	Mouse model	<i>Acinetobacter baumannii</i>	i.p./2 h postinfection, up to 7 days postinfection	(32)
B	Mouse model	<i>Staphylococcus aureus</i>	i.p./6 h postinfection	(33)
B	Mouse model	<i>Klebsiella pneumonia</i> NK-5	i.p./30 min postinfection Intragastric/30 min postinfection	(34)
B	Mouse model	<i>S. aureus</i>	i.p./ 30 min postinfection ; in delayed treatment 0, 1, 2, 3, 4 , 6 h postinfection	(35)
B	Mouse model	<i>Pseudomonas aeruginosa</i> MDR	i.p./45 min postinfection	(36)
B	Mouse model	<i>P. aeruginosa</i>	<i>per os</i> /1 day before, 1 day , 6 days postinfection i.p./1 day before or simultaneously with strain	(37)
B	Mouse model	<i>P. aeruginosa</i> IMPR-Pa	i.p./ up to 1 h ; 3, 6 h postinfection	(38)
B	Mouse model	<i>Escherichia coli</i> ESBL (+)	i.p./ 40 min, up to 60 min postinfection	(39)
B	Mouse model	<i>K. pneumonia</i> MDR	i.p./45 min postinfection	(40)
B	Rat model	<i>E. coli</i> ESBL (+)	s.c./ 7 h and 24 h postinfection	(41)
B	Chickens, calves	<i>E. coli</i> K1	i.m./simultaneously with strain (chickens) i.m./8 h postinfection (calves)	(42)
L	Mouse model	<i>Streptococcus pneumoniae</i>	i.p./1 h postinfection	(43)
L	Mouse model	<i>S. aureus</i> MR	i.p./30 min postinfection	(44)
L	Mouse model	<i>Streptococcus pyogenes</i> <i>S. aureus</i> MR	i.p./3 h postinfection	(45)
L	Mouse model	<i>S. aureus</i> MR	i.p./2 h postinfection	(46)
L	Mouse model	<i>S. pneumoniae</i>	i.p./1 h postinfection (daptomycin + lysin)	(47)
L	Mouse model	<i>S. aureus</i> MR	i.p./1 h postinfection	(48)
L	Mouse model	<i>S. pneumoniae</i>	i.p./1 h postinfection	(49)

i.p., intraperitoneal injection; s.c., subcutaneous injection; i.m., intramuscular injection.

Summary of the data showing the efficacy of phages and their lysins in the treatment of experimentally induced sepsis.

prompt clearance of infection, reversal of the patient's downward clinical course and return to health (51). Those clinical data may suggest that phage therapy may also be efficient—at least in some cases—when administered at later stages of sepsis.

Recently, an important clinical trial evaluating the efficacy of phage therapy in urinary tract infection was announced which may indicate that further progress in the introduction of this treatment is on the horizon (52). The fact that practically all clinical trials reported so far failed to result in a really significant progress in the treatment of sepsis and the data reported in this article suggest that clinical trials on the efficacy of phage therapy in sepsis are urgently needed.

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