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Phage therapy for secondary bacterial infections with COVID-19

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With more than 200 million people affected and 4.5 million deaths so far, the coronavirus disease 2019 (COVID-19) pandemic has become one of the greatest disasters in human history. Secondary bacterial infections (SBIs) are a known complication of viral respiratory infections, and are significantly associated with poorer outcomes in COVID-19 patients despite antibiotic treatments. The increasing antimicrobial resistance (AMR) in bacteria and the decreasing options available in our antimicrobial armory worsen this crisis and call for alternative treatment options. As natural killers of bacteria, phages are recognized as promising alternatives to antibiotics in treating pulmonary bacterial infections, however, little is known about their use for treating SBIs during virus pandemics such as COVID-19. This review highlights the situation of SBIs in COVID-19 patients, and the distinct strengths and limitations of phage therapy for their containment.

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Introduction

Despite of the relatively low incidence of initial bacterial co-infections (≤ 2 days after admission) and of secondary infections (> 2 days after admission) among patients hospitalized with coronavirus disease 2019 (COVID-19) [1^{*}], in severely ill patients secondary bacterial infections (SBIs) are overrepresented and raise ongoing challenges. Growing evidence shows that many COVID-19 patients die of secondary infections,

although most of them receive intensive antibiotic treatments [1^{*},2,3]. In comparison to pneumonia attributable to other respiratory pathogens, severe COVID-19, due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) characteristically causes a longer duration of illness [4^{*}]. Patients with prolonged hospital stays are at increased risk of hospital-acquired multidrug-resistant (MDR) bacterial infections due to nosocomial transmission and inadequate antibiotic treatment. Even worse, the intensive use of antibiotics during the pandemic in turn leads to increased prevalence of MDR bacteria [5,6]. Novel antibacterial agents are urgently needed.

Phage therapy has gained a worldwide renewal of interest following the promising results from recent case studies with customized phages. Since the outbreak of the COVID-19 pandemic, scientists have proposed the potential of phages in different aspects of pandemic containment, such as phage therapy for SBIs [7,8], and phage display for antiviral antibody screening [9^{**}]. However, in contrast to the explosion of studies on anti-SARS-CoV-2 antibodies using phage display techniques [10], little is known about the real-world potential of phages in COVID-19 patients with SBIs.

The application of phage therapy has not been reported during previous virus pandemics. Up to now, our group has published the only paper reporting phage therapy of COVID-19 patients with secondary carbapenem-resistant *Acinetobacter baumannii* (CRAB) pneumonia [11^{**}]. Adaptive Phage Therapeutics (APT), a clinical-stage biotechnology company, has also announced a study treating bacterial co-infected COVID-19 patients with phages [12^{**}]. This opinion review attempts to highlight the situation of SBIs in COVID-19, as well as the strengths and limitations of using natural phages for its control. We also introduce a workflow of phage therapy adapted to COVID-19 patients.

SBIs in COVID-19 patients: why is it a concern?

Secondary infections, mostly bacterial infections, are well-known complications of viral respiratory infections. COVID-19 patients with SBIs were shown to be significantly associated with longer hospitalizations, higher rates of intensive care unit admission, and poorer outcomes compared to those without SBIs [13^{*},14]. A nationwide study in the United Kingdom found that despite the overall rarity of laboratory-confirmed bacterial infections,

recorded positivity rates of cultures from patients admitted to critical care were high—602 (42.1%) of 1429 cultures from sputum, 207 (51.5%) of 402 cultures from deep respiratory samples, and 500 (8.1%) of 6157 cultures from blood [1*]. Of note, this study found no association between bacterial infections and mortality of intensive care unit (ICU) patients, and that contrasts with most studies. In New York City, USA, Kubin *et al.* identified 350 (12%) patients with laboratory-confirmed secondary infections among 3028 hospitalized COVID-19 patients and found that hospital mortality of patients with secondary-/co-infections was significantly higher than the mortality of those without (33% versus 19%) [15]. In Wuhan, China, Zhou *et al.* reported observation in 191 hospitalized COVID-19 patients and found that even though 95% of patients received antibiotics, 27/28 patients with SBIs died [3]. This can be compared with the studies reporting that most deaths in recent influenza pandemics likely resulted directly from secondary bacterial pneumonia [16,17].

SBIs in COVID-19 patients: why is it a challenge?

Antimicrobial resistance-related challenges

Antimicrobial resistance (AMR) had become a major public health problem before COVID-19. Accordingly, the presence of AMR bacteria in healthcare facilities could potentially explain the high rates of SBIs in critically ill COVID-19 patients despite extensive antibiotic treatments. The dominant SBI agents isolated from respiratory and blood samples of COVID-19 patients were those grouped as ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.), a tendency that reflects local epidemiology [1*,15,18]. Antibiotic choice is scanty for those ‘superbugs’, even worse, the use of some ‘last-resort’ antibiotics such as colistin is strictly controlled in consideration of organ toxicity, normal flora disturbance, and AMR induction.

COVID-19 related challenges

Several studies revealed that SARS-CoV-2 pneumonia is associated with a longer duration of illness than pneumonia attributed to other pathogens [4*]. Critically ill COVID-19 patients with prolonged hospital stays were at increased risk of SBIs. Combination immunosuppressive therapies (such as corticosteroids, tocilizumab, and anakinra) that are widely used in COVID-19 patients may have significantly increased the occurrence of bloodstream infection (BSI) in COVID-19 patients [13*]. Patients with BSIs had significantly longer hospitalizations, higher ICU admission and mortality rates compared to those without BSIs [13*]. Moreover, COVID-19-induced pathological processes such as accumulation of mucus, diffuse alveolar damage, impairment of immune signaling, and immune cell depletion may have facilitated

the onset of SBIs and reduced the efficacy of drug treatment [7,19,20].

Initial phage therapy in COVID-19 related SBIs

At the beginning of March 2020, our group applied phage therapy to successfully control an outbreak of secondary CRAB infections in an ICU dedicated to COVID-19 patients in Shanghai, China [11**]. In similarity to other reports, severely ill patients in this ICU were older and predominantly male [1*,13*,21]. Among the eight critically ill patients in the ICU during the study period, four males with difficult-to-treat pulmonary CRAB infections were identified and enrolled. Pulmonary CRAB emerged first in Patient 4 and then successively in the other three patients 18–40 days after their admission to ICU. Patient 2 also acquired a topical infection at the jugular incision of extracorporeal membrane oxygenation (ECMO) intubation. Conventional antibiotic treatment had been tried and failed to suppress CRAB infection. Both phage susceptibility testing and multilocus-sequence typing (MLST) revealed identical profiles of CRAB strains present in these patients. Treatment with a 2-phage cocktail was associated with reduced CRAB burdens in all cases. These results indicated the potential of phages for rapid management of SBI outbreak in COVID-19 patients [11**].

In the USA, a similar battle has begun. In September 2020 the phage-based company APT announced the intention to treat eight CRAB co-infected COVID-19 patients with phages under an emergency Investigational New Drug (eIND) allowance. Just two months later, the U.S. Food and Drug Administration (FDA) granted APT an Expanded Access IND to facilitate the nationwide treatment of COVID-19 patients. The restriction was relaxed from CRAB pneumonia only to pneumonia or bacteremia/septicemia due to *A. baumannii*, *P. aeruginosa* or *S. aureus* (NCT04636554) [12**]. The results of this study have not been released yet. The studies mentioned above are the only two phage therapy studies with SBIs in COVID-19 patients; both send a positive signal that phage therapy may play a role in outbreak containment against those difficult-to-treat SBI pathogens.

Challenges of phage therapy in COVID-19 related SBIs

The rarity of the practice of phage therapy in COVID-19 could be partially explained by the remaining challenges in this area. Phage therapy still faces several hurdles, including safety, efficacy, accessibility, acceptability and regulatory issues, which were detailed in recently published reviews [22–24]. On top of that, SARS-CoV-2 infection now raises additional obstacles. First, given the non-motile property of phages, COVID-19-induced pathologic changes such as airway blockage and thrombus formation may directly block the delivery and dissemination of therapeutic phages to the foci of bacterial

infection. Qin *et al.* showed that bladder-irrigated phages cannot retrogradely reach their target bacteria in the renal pelvis [25]. Second, effective phage therapy may partially rely on a synergism with the patient's immune responses. Unfortunately, COVID-19 was shown to alter immune signaling and deplete immune cells in infection foci [19]. Furthermore, the combination immunosuppressive therapies that are widely used in COVID-19 patients may significantly increase BSI occurrence in COVID-19 patients [13^{*}]. These circumstances raise difficulties for bacterial eradication and consequently, a recurrence of phage-resistant bacteria might be a typical characteristic of phage therapy of COVID-19 related SBIs [11^{**}]. Third, the high biosafety level required in the management of patients infected with SARS-CoV-2 and the wide distribution of the virus over the body undoubtedly complicates the whole process of phage therapy, including pathogen isolation, phage screening, and efficacy evaluation. Although bacteria do not support eukaryotic virus infection, the direct binding of several enteric and respiratory viruses to the surface of various Gram-positive and Gram-negative bacteria was recently reported [26]. Binding of influenza A virus to certain bacterial species was shown to increase the adherence of these bacteria to respiratory epithelial cells in culture [27^{**}], and bacteria may enhance the stability of several enteroviruses [28–30]. Since we don't know if SARS-CoV-2 can bind to bacteria or survive in bacterial colonies, bacterial isolation from samples of COVID-19 patients and the subsequent steps (before inactivation) should be performed in a designated laboratory by professional staff wearing biosafety level III personal protective equipment (PPE BSL-3, Figure 1) [11^{**}]. This will undoubtedly increase the difficulty and cost compared to normal conditions.

Patient care and bacterial culturing are routinely performed at the designated inpatient ward and clinical laboratory by clinical staff wearing biosafety level III personal protective equipment (PPE BSL-3). Ready-to-use phage vials are routinely prepared by using their original host bacteria in the normal phage laboratory and packed in a good manufacturing practice (GMP) approved plant. For customized phage therapy, an established library is transferred to a dedicated BSL-2 laboratory where phage screening and evaluation are performed under BSL-3 PPE conditions. After obtaining the phage-susceptibility result, phage(s) with optimal lytic characteristics are selected and the corresponding vials are transferred to the PPE BSL-3 phage laboratory for killing-efficiency inspection. Qualified phage vials with high titers against the target bacteria are then delivered to the inpatient ward for phage therapy. For empirical phage therapy, fixed-composition phage cocktails with broad-spectrum antimicrobial properties against the epidemic strains can be applied for emergency use.

'SIP experience' of phage therapy in COVID-19 related SBIs

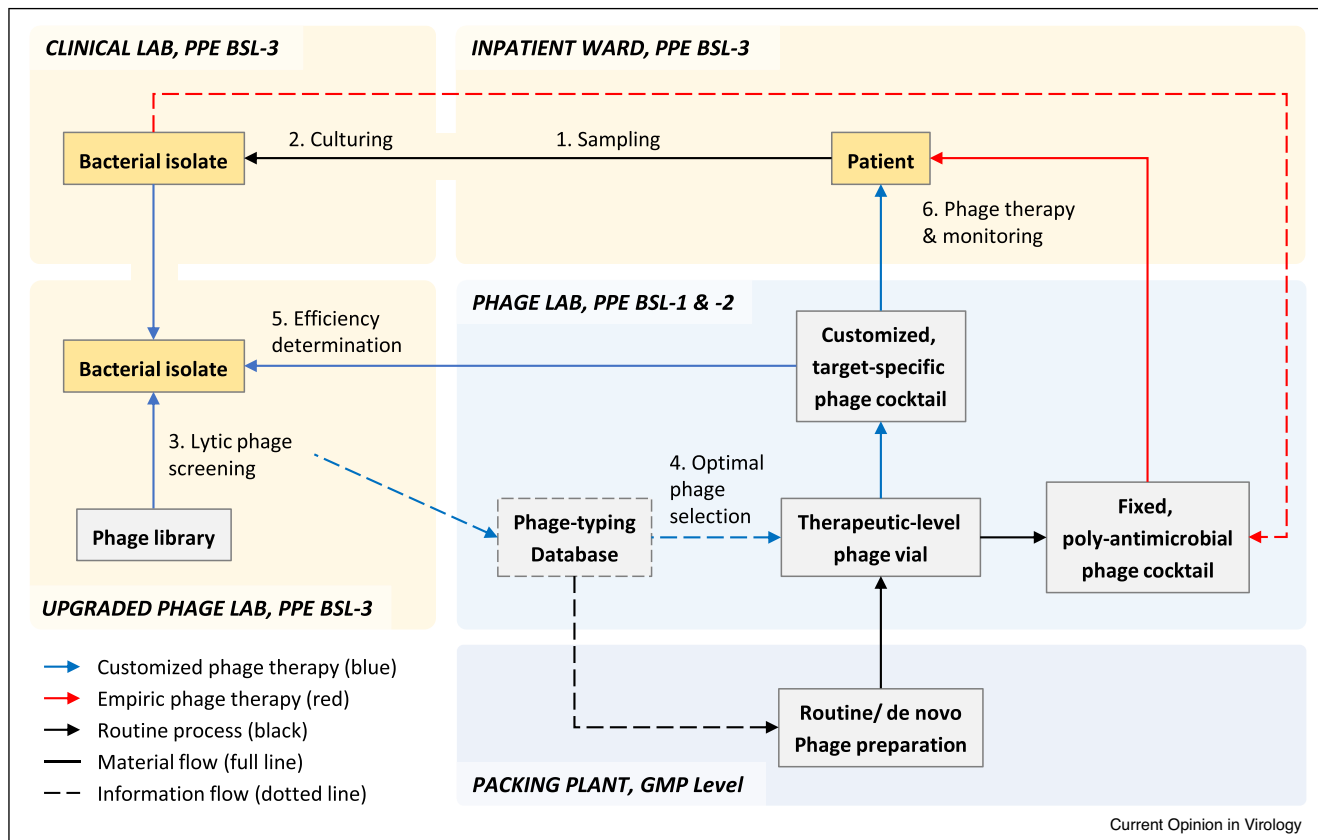
A practicable workflow

Since the emergence of the first wave of COVID-19 patients in Shanghai, our group at Shanghai Institute of Phage (SIP) started to increase the storage of ready-to-use phage vials which target the most common hospital-acquired pathogens, such as the ESKAPE pathogens. This strategy greatly accelerated phage delivery for critically ill COVID-19 patients requiring rapid initiation of treatment. Meanwhile, we established a workflow based on the collaboration of five function zones requiring different levels of PPE. As shown in Figure 1, patient care and bacterial culture were performed in the inpatient ward and clinical laboratory according to the standard procedures in a COVID-19-designated hospital. A special area of the clinical laboratory was isolated for phage screening and efficiency determination under BSL-3 PPE conditions. Ready-to-use phage vials were prepared with phage routinely amplified by growth in the original host bacterium in the normal microbiology laboratory. The vials were packed in a good manufacturing practice (GMP) certified packing plant. By taking advantage of the material flow (from lower BSL zones to higher BSL zones) and the reverse information flow, qualified phage vials can be rapidly selected and delivered to the inpatient ward for phage therapy. For epidemiological purposes, bacterial isolates were routinely phage-typed and this database is also useful for the preparation of adequate therapeutic phages and the assembly of fixed-composition, broad-spectrum phage cocktails for emergency use (Figure 1) [31^{*}].

An *in vitro* strategy

Our phage therapy cases represent a typical nosocomial outbreak and management of secondary CRAB pneumonia in an ICU with critically ill COVID-19 patients [11^{**}]. We observed that when an *A. baumannii* strain was challenged *in vitro* and *in vivo* with the same (first line) phage, the *in vitro* induced and *in vivo* selected phage-resistant *A. baumannii* isolates displayed closely matched phage susceptibility profiles. Therefore, we designed a cocktail consisting of the first line phage, to which a second phage, which targeted the *in vitro* induced first line phage-resistant *A. baumannii* isolate, was added. The *in vitro* analysis indicated a synergistic effect between the first-line and the second-line phages in suppressing the recurrence of target bacteria within eight hours. However, the clearance of CRAB was only observed in two of five courses of phage therapy using the cocktail; in the others, the bacteria recurred and were resistant to the cocktail [11^{**}]. This may have been partially due to impaired host immune responses which failed to facilitate phage-mediated bacterial elimination [32]. A prolonged phage-bacteria incubation and more extensive exploration of different phage combinations might lead to the identification of a more potent phage cocktail for curbing the anti-phage

Figure 1



Workflow of phage therapy for SBIs in COVID-19 patients at Shanghai Institute of Phage (SIP).

resistance associated with phage therapies. Additional information from tests of phage-antibiotic synergy can be helpful but adds extra load and hours of work [33,34].

A safety reminder

Host immune responses to therapeutically applied phages are controversial and may vary depending on the phages, delivery routes, or host immune status [35–37]. Previous studies suggest lower risks of phage-induced endotoxin release and inflammatory response than incurred by antibiotics [38,39], however, we observed in one COVID-19 patient a transient fever and IL-6 & IL-8 storm four hours after phage inhalation. Our observation is consistent with a recent report of a transient fever and stimulation of host innate immunity genes associated with intravenous phage therapy in a 7-year-old child [40*]. Therapeutic phages might trigger human immune responses directly as antigens or indirectly by the rapid lysis of the targeted bacteria. Phage-specific antibodies were found to be stimulated after intravenous phage injection and may impair the outcome of long-period phage therapy [35]. Phage expansion may also aggravate intestinal inflammation and colitis [41].

Taken together, we recommend that risk prevention measures against a cytokine storm should be considered during phage therapy in critically ill patients.

Conclusion

Despite advances in vaccination and clinical management, the end of the COVID-19 pandemic is not nearly in sight yet. Patients with severe COVID-19 will continue to occupy hospitals and ICUs for the foreseeable future. The increasing number of AMR bacteria and our decreasing capacity to control them render us more vulnerable to SBIs arising in COVID-19 patients during both this and the next pandemic. Alternative antimicrobial strategies are urgently needed. Despite the limited practice of phage therapy for SBIs in COVID-19 patients, the pioneers both in China and the USA sent a positive signal that it has a great potential for management of those difficult-to-treat bacterial infections in severely ill COVID-19 patients. Nevertheless, challenges remain and several important questions need to be investigated. First, what are the pharmacodynamics and pharmacokinetics of nebulized and intravenous phages in severely ill COVID-19 patients, and which delivery route is the best?

Second, how significant are phage induction of, and influence on, host inflammatory responses, and are the effects phage-specific or patient-specific? Third, does SARS-CoV-2 hitch a ride with bacteria to facilitate its distribution? If this is substantiated, manipulation of secondary bacteria from COVID-19 patients will certainly require high biosafety levels.

Conflict of interest statement

Nothing declared.

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