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Review

The potential of bacteriophage therapy in the treatment of paediatric respiratory infections

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Educational aims

The reader will come to appreciate: the basic biology of bacteriophage, their historical context in medicine and the growing therapeutic potential that bacteriophage may play in the future.

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ABSTRACT

The looming antibiotic resistance crisis is forcing clinicians to consider alternative approaches to treating bacterial infections. As the window of use for current antimicrobial agents becomes ever narrower, we consider if looking back will now be the way forward. Conceptually, phage therapy is simple and specific; a targeted treatment to control bacterial overgrowth. In this article we discuss bacteriophage and potential use in future therapy.

INTRODUCTION

'Insanity is doing the same thing over and over again but expecting different results." – Rita Mae Brown, 1983.

In paediatric respiratory medicine, particularly in cystic fibrosis (CF) patients, the emergence of multi-drug resistant (MDR) bacterial infections increases duration of hospital admissions and significantly affects patient morbidity and mortality [1,2].

MDR infections often require combinations of increasingly toxic antimicrobial agents. Patient intolerance of the side effect profiles of these treatment regimens is often the main factor associated with treatment failure. Moreover, current treatment strategies for some MDR organisms give mixed results. We often use antibiotic guidelines based on evidence that was gathered 30 years ago with a worrying lack of scrutiny to changes in bacterial taxonomy. When intense eradication fails, we accept colonisation, frequent respiratory exacerbation, and lung function decline as the norm for this group of patients [3,4].

Microbiologically, infections reflect a polymicrobial environment with a limited number of genera and species becoming dominant, generally those considered the main pathogen(s). We understand little about the complex populations, interactions between different species of bacteria, fungi and viruses and how population disruption affects the overall community and the patient [5,6]. Yet, our response is to use pharmacologically derived/modified antibacterial agents with broad spectrums of activity, not only targeting the rogue dominant strain, but essentially cleansing the commensal community within the lung (and gut) at the same time. A reduction in microbiome diversity has significant detrimental effects on severity and frequency of respiratory exacerbations and higher risk of morbidity/mortality [7].

The combination of the often intolerable side effects of current antibiotic regimens, antibiotic resistance and the poorly understood adverse effects of broad-spectrum antimicrobial agents on commensal microbiota mean that there is an urgent need for a new approach to the treatment of MDR paediatric respiratory infections. Bacteriophage, generally known as phage, are an alternative antimicrobial which combine a promising side effect profile with the ability to target specific bacterial species, or even strains [8,9]. Relative to antibiotics, phage are 'smart' antimicrobials that offer clinicians an unprecedented opportunity to precisely address pathogenic species [9]. The concept of using bacteriophage to treat bacterial infection, known as phage therapy, was mooted over

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100 years ago [10,11]. Although used in the early 20th Century [12], phage therapy declined sharply following the discovery of penicillin [13] and mass production of antibiotics but increasing antibiotic resistance is driving renewed interest.

WHAT ARE BACTERIOPHAGE?

Bacteriophages are ubiquitous "bacterial viruses" present in high numbers in all known ecosystems [14]. Most described bacteriophages belong to the order Caudovirales (tailed bacteriophages) and are divided into three families: Myoviridae with long contractile tails, Siphoviridae with long non-contractile tails and Podoviridae with short non-contractile tails. They share a common icosahedral capsid "head" structure that contains double-stranded linear DNA and a caudal "tail" part with structures for bacterial adhesion [15].

In nature, there are two distinct phage replication cycles (Fig. 1). Lytic phage replication takes approximately 30–60 minutes and results in death of the host bacterial cell. In contrast, temperate (lysogenic) phages integrate into the DNA of the host bacterial cell, where they are known as a prophage, and are passively replicated during bacterial cell division. In response to various factors, a prophage can be induced to excise itself from the host DNA and enter the lytic replication cycle. Temperate phages therefore have significant potential to transfer genes between bacterial hosts, even increase virulence in some cases [16], and are thus less useful therapeutically. The balance of phage types in natural systems, such as aquatic environments, the soil, or the human host, is an important factor in environmental bacterial population control and evolution [17].

HISTORIC MEDICAL USE OF BACTERIOPHAGE

In the early 20th century "filterable and transmissible bacterial lyses" were co-identified by Felix d'Herelle and Frederick Twort [10,11]. The term 'bacteriophage' was proposed by d'Herelle and literally means 'bacteria eater'. These 'filterable agents' were quickly identified as possible treatments for bacterial infections such as cholera and dysentery [18]. The 1920 s and 30 s saw extensive use of phage for the treatment of bacterial infections, known as phage therapy, in the geopolitical West, East and Latin America [9,19]. Some of the first commercially produced phage preparations were made in D'Herelle's Paris laboratory and marketed by a company that would later become the well-known French brand L'Oreal [20]. However, there were increasing concerns about efficacy of phage therapy. As phage infect bacteria in a species- (and sometimes even strain-) specific manner, *in vitro* assessment of phage activity against a target bacterium is required to guide phage selection. Ironically, over-enthusiasm in the efficacy of phage resulted in injudicious use of phage not appropriate to the pathogen, creating doubts about effectiveness. There were also concerns about the nature of phage; phage particles were not observed by electron microscopy until 1939, two decades after they were first identified, and there were also manufacturing challenges [21]. Together these factors led to a decline in interest in phage therapy, which was accelerated by the mass production of antibiotics, which were easier to make, market and use.

Over the last two decades phage have re-emerged as possible agents to combat both the rise of MDR bacteria and lack of new antimicrobial agents being developed by the pharmaceutical industry [22]. The US National Institute of Allergy and Infectious Diseases has cited phage as key agents in the fight against MDR infections. In 2016, the Review on Antimicrobial Resistance (AMR) predicted that globally 10 million deaths will be attributable to AMR each year and highlighted the importance of alternative antimicrobial strategies, including phage therapy [23]. Currently, it is estimated that the cost of AMR in the United States alone is $55 billion [24].

BACTERIOPHAGE AS THERAPEUTIC AGENTS

Naturally occurring phage have several advantages over conventional antibiotics (Table 1), including low inherent toxicity, suitability for patients allergic to antibiotics and the ability of some phage to degrade biofilms, the polysaccharides matrices produced by certain bacteria that typically underlie recalcitrant infection [25]. Moreover, phage act independent of antibiotic resistance and some antibiotic/phage combinations can have a synergistic antimicrobial effect [26]. Phage also exhibit auto-dosing, where the number of phage increases or decreases relative to the number of bacterial hosts; when no host bacteria remain, no phage remain [27]. Phage also replicate, and therefore can evolve, faster than bac-

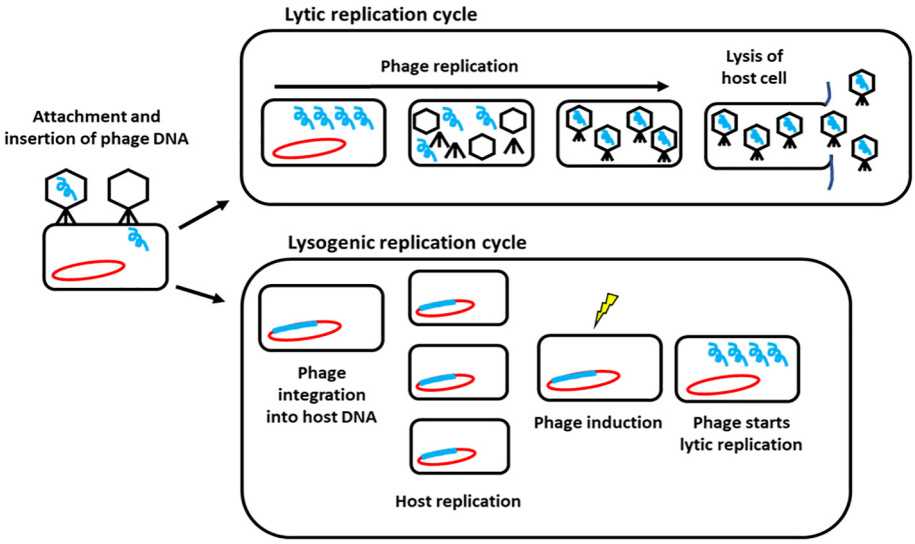

Fig. 1. The lytic and lysogenic cycles of phage replication.

Table 1
Advantages and caveats of phage therapy.

Advantages	Caveats
Efficient bacterial clearance – independent of antibiotic resistance	Requires lytic phage *– although these can be easily selected for*
No notable side effects	Phages often have a narrow host range *– phage cocktails can be used to broaden therapeutic application*
Suitable for patients with renal impairment, immunodeficiency or allergy to antibiotics	Bacteria can become resistant to phage *– although phage exist in a co-evolutionary arms race with bacteria* [45]
Minimal impact on commensal flora	Cultural lack of familiarity
Auto-dosing	
Versatile formulations	
Some phage can degrade biofilms	
Potentially synergistic with antibiotics	
Can be fast and cheap to produce (with improving technology)	
Potential for personalised medicine	

teria, turning the antimicrobial tables where we are so often used to seeing bacteria out-evolve chemotherapeutic antibiotics. Given the high level of phage host specificity, collateral damage to other bacterial genera/species is also limited, leaving the wider microbiome intact [28].

While an advantage in many respects, the narrow host range of many phage means that phage cocktails may be required [29]. Such cocktails require careful composition and the safety and efficacy of these preparations needs to be verified. Merabishvili *et al.* describe the design of bespoke cocktails of lytic phages which were specially assessed for stability, pyrogenicity, sterility, cytotoxicity and specific antibacterial activity against the targeted bacteria. Genetic analyses were also used to confirm the lytic nature of the phage, the absence of lysogenic phage and the absence of toxin-coding or antibiotic resistance genes that might otherwise be introduced into pathogenic or commensal bacteria [30].

Another advantage of phage therapy is that, in general, the lag time from phage discovery to therapeutic use can be measured in weeks and tens of thousands of pounds, relative to the years and millions of pounds required for a single antibiotic. This also means that, relative to antibiotic development, development of phage therapeutics is more sustainable and has a lower environmental impact. Moreover, unlike antibiotics, there is little concern about the release of naturally occurring phage used for therapy into the environment [31].

The interaction between phage and the immune system also requires consideration. An in-depth review of this topic has recently been published elsewhere [32]. Humans exist, and have evolved, in constant contact with phages. It is therefore unsurprising that phage appear to be remarkably well tolerated immunologically. Virome studies have identified high abundance of phage within immunologically privileged sites, including the cerebrospinal fluid (CSF) with no obvious inflammatory consequence and apparent tolerability [33]. Phage can elicit a humoral immune response. For example, administration of intravenous phage PhiX174 has been used to evaluate humoral immune responses of patients with immunodeficiency [34]. Natural exposure to environmental phage is responsible for the presence of anti-phage antibodies in healthy volunteers [35,36]. From the perspective of therapeutic use, anti-phage antibodies can interfere with treatment, as recently observed in a bronchiectasis patient with refractory *M. abscessus* infection [37]. However, there is also evidence suggesting that high titres of anti-phage antibodies do not result in an unsatisfactory therapeutic outcome [35]. The influence of anti-phage antibodies on the outcome of phage therapy will likely reflect a combination of factors, including the immunogenicity of the phage(s), route of administration and dosing schedule [38].

The pharmacology of phages has recently been reviewed elsewhere [39]. Following intravenous administration, phage distribution is widespread throughout all organ systems. Clearance, however, is rapid and considered to reflect degradation of phage by the reticuloendothelial system in the liver and spleen, with most phage being removed within the first hour following infusion [40]. However, a murine model indicated that populations may persist for a number of days [41] suggesting that prophylactic treatment has a potential role [42]; notably oral prophylactic phage was historically used to prevent dysentery outbreaks in the former Soviet Union.

It is important to note that bacteria can, and do, become resistant to phage. However, such is the diversity of phage in the environment that it is almost certain that a phage can still be found that will lyse a resistant bacteria. For example, when in 2017 an MDR *Acinetobacter baumannii* demonstrated resistance to a phage being used intravenously, the team treating the patient were able to isolate a new phage with activity against the bacteria from wastewater [43] demonstrating the potential for personalised phage cocktails to treat unusual, refractory infections.

Despite the potential benefits, use of phage as therapeutic biological agents may cause some anxiety. This largely arises from Western unfamiliarity with phage treatment, although there is evidence that patients are receptive to the idea of phage therapy [44]. Just as society has come to accept the concept of 'good bacteria', so must we also come to realise the beneficial role of phage as 'good viruses'. The main disadvantages relate to difficulties in identification of appropriate lytic phage with high virulence and a wide enough species/strain range to be useful in different patients with different strains of infecting bacteria (Table 1). However, careful phage selection and bespoke phage "cocktails" can address many of the disadvantages.

BACTERIOPHAGE IN RESPIRATORY DISEASE

Phage therapy has previously been used in a variety of, predominantly surgical, specialities, including for the treatment of burn wounds, orthopaedic, vascular and soft tissue infections [46–50]. Use within respiratory medicine has focused on specific organisms in the context of cystic fibrosis (CF) or chronic respiratory infection (Table 2). There is also substantial interest in phage therapy for *Mycobacterium tuberculosis* [51]. While thirteen clinical or safety trials of phage therapy have consistently demonstrated safety and, to varying degrees, efficacy of phage therapy [28,50,52–62], there has not yet been a clinical trial of phage for the treatment of respiratory infection, although a clinical trial in CF patients treated with nebulised anti-Pseudomonas phage is underway in the US (Cystic Fibrosis bacteriophage Study at Yale (CYPHY) https://clinicaltrials.gov/ct2/show/NCT04684641)

The impact of phage therapy in respiratory disease is promising. It offers potential for highly specific antimicrobial therapy with a seemingly far superior side-effect profile to current chemotherapeutic antimicrobial regimens [75]. By screening a patient's specific bacteria against a collection of therapeutic phage, there exists powerful potential to rapidly generate personalised phage cocktails for patients with difficult to treat infections (such as *Mycobacterium abscessus*). We will briefly consider the progress of phage therapy for major, and typically recalcitrant, paediatric respiratory pathogens.

Table 2
Reports of phage therapy in respiratory medicine.

Respiratory condition	Target organism(s)	Duration and route of administration	Phage used as adjunct to appropriate antibiotics?	Outcome	Citation
COPD N = 1 Age: 88	*Acinetobacter baumannii* Isolate persisted despite one month's antibiotic therapy with, variously, ceftazidime, ciprofloxacin, amikacin.	Ten phage cocktail Nebulized twice daily for 16 days. Up to 5×10^{10} PFU.	Yes.	Resolution of infection and improved lung function. Safe.	[63]
Bronchiectasis N = 1 Age: 81	*Mycobacterium abscessus* Five-year history of multidrug resistance.	Three phage cocktail IV twice daily for six months. 1×10^9 PFU/ml.	Yes.	Reduced *M. abscessus* count after 1 month. Antibody-mediated phage neutralization reduced efficacy. Safe.	[37]
COVID-19 secondary bacterial infection N = 4 Ages: 62–81	*Acinetobacter baumannii* Carbapenem-resistant isolates.	Two phage cocktail Nebulised: two 10 ml doses given with a 1 h interval 10^8PFU/ml	Yes.	Two patient chest radiographs improved. Infection at jugular incision for ECMO resolved by topical phage therapy. Patient three became culture negative. Patient four improved and was discharged from ICU 7d post-phage. One patient had raised IL-6 and IL-8 4 h after phage administration. The authors suggested this may have been linked to COVID-19 not phage.	[64]
VAP N = 1 Age: 77	*Pseudomonas aeruginosa* Multi-drug resistant isolate.	Four phage cocktail Nebulised (10^9 PFU/ml) and IV (10^8 PFU/ml) twice daily for 7 days	Yes.	Patient was culture negative after day 4 of phage therapy and progressed to resolution and discharge from hospital. Remained culture negative at 6 months. Safe.	[65]
Post-transplant infection N = 3 Ages: 28–67	*P. aeruginosa* (n = 2) *Burkholderia dolosa* (n = 1) Multi-drug resistant isolates.	*Pseudomonas*: Ten phage, three cocktails IV +/- nebulized. IV: 4 times daily. Nebulised: twice daily. 4–8 weeks. 10^7 – 10^9 PFU/ml. *Burkholderia*: 1 phage $>10^6$ PFU/ml IV once daily for 2 weeks and twice daily for 4 weeks	Yes.	*Pseudomonas* patients were able to be discharged from hospital off ventilator support. The *Burkholderia* infection initially improved but relapsed and the patient died. Safe.	[66]
Bronchopneumonia, empyema N = 57 Ages: N/A	*Staphylococcus aureus, Escherichia coli, Klebsiella, Proteus, Pseudomonas* Multi-drug resistant isolates.	No details of the phage used. Administration was oral three times daily. Adults 10 ml, children 5 ml.	Unclear.	82% full recovery and culture-negative, 18% no effect.	[67]
CF N = 1 Age: 26	*Pseudomonas aeruginosa*	Four phage cocktail 8×10^8 PFU/ml IV four times daily for 8 weeks	Yes.	Infection resolved. Safe. Proceeded to transplant.	[68]
CF N = 1 Age: 17	*Achromobacter xylosoxidans* (infected from age 12) Multi-drug resistant isolate.	Two phage cocktail Once daily nebulised and twice daily oral for 20 days. Course repeated quarterly for 12 months. 3×10^8 PFU/ml	Yes.	Substantial improvement in lung function. No comment on safety.	[69]
CF (post-transplant) N = 1 Age: 15	*Mycobacterium abscessus* Multi-drug resistant isolate.	Three phage cocktail IV twice daily for > 32 weeks. 10^9 PFU/dose.	Yes.	Substantial clinical improvement. Safe.	[70]
CF (post-transplant) N = 1 Age: 12	*Achromobacter xylosoxidans* Pan-resistant isolate.	Treatment one: Three phage cocktail Nebulised, three times a day for 3 days. 4×10^9 PFU/ml. Treatment two: An additional phage was added to the cocktail. Admitted for 30 ml in each lobe instilled via bronchoscopy and discharged with further nebulization 3 times a day for 14 days.	Yes – although isolate showed pan-resistance to antibiotics.	Progressive improvement in lung function and decline in *A. xylosoxidans* counts, until culture negative six months later. Safe.	[71]
CF N = 1 Age: 10	*Achromobacter* spp. Pan-resistant isolate.	One phage. IV once daily for 2 weeks.	Yes – although isolate showed pan-resistance to antibiotics.	Significant improvement in lung function. Culture negative at 8- and 16-weeks post treatment. Safe.	[72]

(*continued on next page*)

Table 2 (*continued*)

Respiratory condition	Target organism(s)	Duration and route of administration	Phage used as adjunct to appropriate antibiotics?	Outcome	Citation
CF N = 1 Age: 7	*Pseudomonas aeruginosa* and *Staphylococcus aureus* Multi-drug resistant isolates.	Pyophage cocktail. Nebulised on nine occasions at 4–6 week intervals. Five nebulised administrations included an anti-Staphylococcal phage.	Yes.	The patient became culture negative. Patient still being treated at the time of report, no significant improvement in X-ray findings at the time. No comment on adverse effects.	[73]
CF N = 1 Age: 5	*Pseudomonas aeruginosa* and *Staphylococcus aureus* Multi-drug resistant isolates.	Pyophage cocktail. and used for nasal and pharyngeal rinsing. Three times daily for 6 days. A second round of treatment was performed for 10 days one month after the initial treatment. A third round followed after a further one-month interval.	Unclear.	Significant clinical improvement. No comment on adverse effects.	[74]

PSEUDOMONAS AERUGINOSA

Pseudomonas aeruginosa is "a phenomenon of bacterial resistance [76]" and therefore a key target for respiratory phage therapy (Fig. 2). Initial animal models in *P. aeruginosa* infection in cystic fibrosis have reported "successful" eradication with phage therapy [77]. As summarised by Pires *et al*, using one or more phage for therapy in animal models can result in effective reduction in viable *P. aeruginosa* levels [78,79]. Notably, *P. aeruginosa* can become resistant to phage, and multi-phage resistant pseudomonal strains have been documented [80]. However, resistance can be mitigated by the use of multiple phages, analogous to antibiotic combination therapy [81]. Reassuringly, where resistance emerges, the diversity of phage in the environment means that an effective phage is likely to exist, but further phage isolation may be required, e.g. from wastewater. Some phage are also able to destroy the *P. aeruginosa* biofilm, enhancing their antimicrobial efficacy [82].

Clinically, respiratory *P. aeruginosa* infections in CF patients have been successfully treated without adverse effects, including in post-transplant patients (Table 2). This is particularly encouraging and warrants substantial attention from funders in this area. The success of phage therapy in post-transplant infections, without adverse effects, emphasises that, by definition, phage do not pose an infectious risk to humans. Moreover, success of phage therapy in post-transplant infections has also been observed in other clinical contexts, including liver and renal transplants [83,84].

MYCOBACTERIUM ABSCESSUS

The potential of phage therapy to target *M. abscessus* was highlighted in 2019, with successful treatment of a post-transplant CF patient at Great Ormond Street Hospital, London. *M. abscessus* is a significant clinical challenge, particularly for CF patients, and the potential for phage therapy against *M. abscessus* has recently been reviewed elsewhere [85]. Mycobacteria are intracellular pathogens. While free phage are able to target extracellular bacteria, clearance of intracellular bacteria remains a challenge, albeit one that liposomal administration might address [85].Due to the nature of Mycobacterial infections, substantial clinical progress is likely to require prolonged phage therapy. This is reflected in the 6- and 8-month treatment regimens given in the two cases documented thus far (Table 1). Such prolonged therapy may elicit anti-phage antibodies, which have been observed to neutralise phage activity. The effect of neutralising antibodies could potentially be addressed by changing the phage used for therapy during treatment. However, the presence of pre-treatment anti-phage antibodies need not be considered a contraindication to therapy [37].

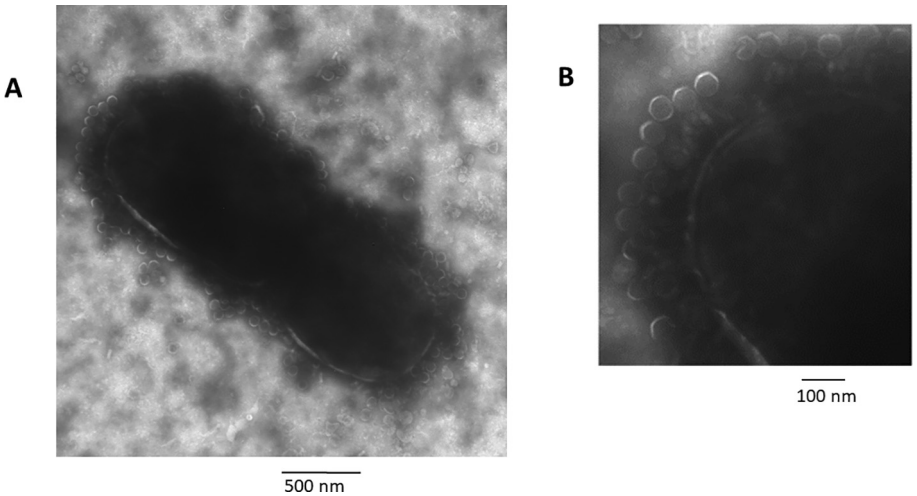

Fig. 2. A. Electron micrograph of *Pseudomonas aeruginosa* (PAO1) engulfed by lytic phage. B. Same image at higher power of magnification.

OTHER ORGANISMS

As shown in Table 2, phage therapy has also been successfully used to treat respiratory infections caused by antibiotic resistant *Acinetobacter* (n = 5), *Achromobacter* (n = 3), *Staphylococcus* (n = 2) and *Burkholderia* (n = 1) species in human subjects. Phage therapy also has potential against other recalcitrant pathogens, including *Stenotrophomonas maltophilia* [86]. The efficacy of aerosolised phage therapy for treatment of mice infected with *Burkholderia cepacia* complex has also been demonstrated [87].

WHY HASN'T PHAGE THERAPY PROGRESSED BEFORE?

If phage therapy is so promising it is reasonable to consider why it hasn't progressed further already. Several factors have inhibited interest in phage therapy. First, and quite simply, antibiotics have been sufficient. However, the antibiotic resistance crisis has brought into focus the need for alternative antimicrobial strategies. Second, aside from the usual commercial disincentives for developing anti-infectives, the use of naturally occurring phage for therapy is not commercially attractive. Naturally occurring phage are discoveries and not themselves protectable and phage are also easily copied. Third, phage therapy, the use of a live virus to treat a bacterial infection, presents a cultural barrier to both clinicians and patients who may, despite reassuring evidence, retain an aversion to administration of phage. However, diabetic foot infection patients have been found to be very receptive to the prospect of phage therapy, particularly the prospect of reducing their exposure to the side effects associated with antibiotics [44].

OUTSTANDING CONSIDERATIONS

While phage therapy has the potential to transform how we treat infections in respiratory medicine, and medicine more broadly, there are several considerations which remain to be addressed. However, as demonstrated by the cases in Table 2, these considerations should not, against the backdrop of the broader body of evidence in favour of the safety and efficacy of phage therapy [40,46,47], prevent the use of phage as a treatment option when antibiotics are proving ineffective.

As is evident from Table 2, there is no defined treatment regimen, with duration, dose and route(s) of administration varying on a case-by-case basis. Practically, options for administration include via nebuliser, intranasal, direct administration via bronchoscopy, oral and intravenous (Table 2). The 'best' method(s) of administration have yet to be determined. Unlike chemotherapeutic antibiotic therapy, the biological nature of phage therapy will mean treatments and treatment plans are more likely to need to be personalised. The particulars of phage therapy will generally reflect a combination of the pathogen(s) present, phage(s) and nature of the infection(s) being treated in a given patient. Although promising, phage therapy is not a panacea and treatment failure has generally been observed to result from bacterial resistance to phage, insufficient bacteria to sustain phage replication and neutralising anti-phage antibodies [37,57,88].

There is excitement about the potential for combined phage and antibiotic treatment to provide a synergistic therapeutic effect. However, this is likely to vary between phage/antibiotic combinations and will be complex to unravel definitively [89], although sub inhibitory concentrations of antibiotics may in fact foster phage productivity; this is termed phage-antibiotic synergy (PAS) [26]. Lastly, phage therapy offers us the opportunity to precisely manipulate the pulmonary microbiome. Current evidence suggests that phage do not adversely affect the commensal microbiota in other body systems [90]. Whilst the effect of long-term phage use on commensal flora remains to be established, this should be contrasted in proportion with the well-known obliterative effects of many antibiotics on commensal microbiome [91].

CONCLUSION

Phage therapy has the potential to transform the management of paediatric respiratory infections. There have already been multiple reports of phage being successfully used to treat antibiotic resistant infections, with excellent results. It is conceivable that, in a few years, paediatric respiratory patients with complex infections may be benefitting from phage therapy, given alongside or instead of antibiotics. Depending upon infection site and severity, upon admission patients may be given a nebulised, oral or intravenous phage cocktail, targeting likely pathogens, such as *P. aeruginosa*, based on knowledge of locally circulating strains. Such cocktails could be given empirically but laboratory analysis of patient's own pathogen(s) and their sensitivity to the cocktail might also be needed. For some, a standard cocktail will be sufficient, but others will have bacteria that are not covered by the cocktail or that have developed resistance to the frontline phage. These patients could be provided with personalised phage therapy. A sample of their pathogen(s) will be sent off to a central national phage centre where the bacteria are exposed to a collection of phage to determine which phage(s) best kill the bacteria. A personalised formulation can then be prepared. This combination of cocktail and personalised therapy has worked successfully for many years in Georgia [92]. Prolonged phage therapy may elicit bacterial resistance to phage(s) or neutralising anti-phage antibodies. In either event, further adjustment to the phage(s) and/or route of therapy could be made. A particularly attractive feature of phage therapy for patients is that the strong safety profile provides the potential for home-based or outpatient therapy. Regardless of the particulars of phage therapy, it will be important to work closely with adult respiratory specialists to ensure that paediatric patients benefitting from phage therapy are offered ongoing access to phage when entering adult services.

DIRECTIONS FOR FUTURE RESEARCH

1) Broadly characterise the microbiological profile of respiratory infections to determine and prioritise future targets for phage therapy development
2) Investigate the effects of long-term phage use on the commensal microbiota
3) Work towards clinical trials of phage therapy for respiratory infections in the UK

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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