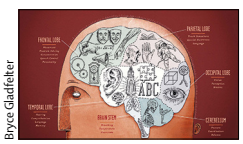
Cover artist for 2019



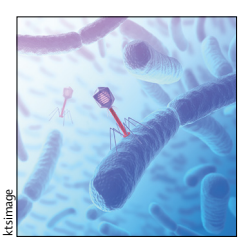
Bryce Gladfelter

The new artist creating the cover images for *The Lancet Infectious Diseases* for 2019 is Bryce Gladfelter, who replaces Kouzou Sakai from the Folio Illustration Agency. We are grateful to Kouzou for his imaginative take on the often difficult articles that were proposed as an inspiration for his images. Working with Kouzou has been a great pleasure for me, and we have tried over the months to include animals, our shared interest, in each cover. For 2019, Kouzou will be the cover artist for *The Lancet HIV*, and we wish him the best in his new adventure in *The Lancet* family.

Bryce currently resides in Philadelphia, PA, USA. An adventurer at heart, Bryce Gladfelter has traversed the Rockies on a llama and crossed paths with grizzlies in Alaska. He honed his skills in the arts during hours spent drawing on trains and buses, people watching in markets, and wandering the natural world. His original style and his imaginative creation of labels for beer bottles have caught our attention, and we look forward to a year of collaboration to create new distinctive covers for *The Lancet Infectious Diseases*.

Marco De Ambrogi
The Lancet Infectious Diseases

Phage therapy 2.0: where do we stand?



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See Articles page 35

In *The Lancet Infectious Diseases,* Patrick Jault and colleagues[1] report the results of the PhagoBurn study investigating the efficacy and tolerability of a cocktail of bacteriophages against *Pseudomonas aeruginosa* in infected burn wounds.

To my knowledge, this is the first well designed randomised controlled trial on the efficacy of phage therapy of burn wounds in humans, which is a major achievement in itself. In the past decade, interest in phage therapy has been revived in the medical literature, which might be because of the increasing problem of multidrug-resistant bacteria and the promising results from case studies and not so well designed studies from the 1930s and 1940s. However, phage therapy has several drawbacks and many unsolved questions still exist that will make it difficult to estimate its value as a therapy for the future.

Safety is one of the main issues in the use of phages since they are living organisms. They consume specific bacteria by self-replication and they die when the bacteria are no longer available. But what if these phages could switch to consuming other so-called good bacteria?

The primary outcome of Jault and colleagues' study[1] was the time to reduction of bacterial burden in infected burn wounds by use of a topically administered cocktail 12 natural lytic anti-*P aeruginosa* bacteriophages compared with sulfadiazine silver as the standard of care. The authors found that the primary endpoint was reached in 144 h in the page therapy group versus 47 h in the standard of care group (hazard ratio 0·29, 95% CI 0·10–0·79; p=0·018). However, one should note that this outcome was only assessed in 25 participants, 12 in the phage therapy group and 13 in the standard of care group, and that wound healing, scarring, and quality of life were not outcome parameters.

Production and stability of a phage solution is still a problem. Off the shelf use of a universal active phage solution is far away and has the disadvantage of non-specific action to some, but not all, bacterial species. Even for specific strains of bacteria within one species, a specific active phage is needed, and testing for the specific phage needed by composing a so-called phagogram in advance would be very time consuming and expensive.

Frequently, many different bacterial species can be present in one colonised or infected wound, and up to 20% of pathogenic bacteria are resistant to commercially available phage solutions.[2] To date, the side-effects concerning the presence of endotoxins and other bacterial remnants in phage solutions are unclear, even if only applied topically. This issue also makes systemic treatment difficult or impossible. What is also unknown is the reaction of the human immune system to the phages; could their repeated application provoke an allergic reaction?

More needs to be learnt about what the effect of frequently used phage-based products are on the human

body, or what the effect of specialsied burn wound care would be on the activity of the phages. In-vitro studies have shown a fast and strong inhibitory effect on phage activity by sulfadiazine silver and mupirocin creams.[3]

On the basis of current evidence I would still be prudent in advocating phage therapy as a solution to the global problem of multidrug-resistant bacteria. More high-quality research is needed to answer the questions raised about the use of phages.[4] Jault and colleagues' study shows that phages have some action on the colonisation of bacteria in humans, but whether the efficacy is good enough to have an effect on infection is yet to be shown.

Roelf S Breederveld
Department of Surgery, University Hospital Leiden, Burn Center Red Cross Hospital Beverwijk, Beverwijk 1942LE, Netherlands
breedrs@gmail.com

I declare no competing interests.

1 Jault P, Leclerc T, Jennes S, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a multicentre, controlled, randomised, double-blinded phase 1/2 clinical trial. *Lancet Infect Dis* 2018; published online Oct 3. http://dx.doi.org/10.1016/S1473-3099(18)30482-14.
2 Kutter E, De Vos D, Gvasalia G, et al. Phage therapy in clinical practice: treatment of human infections. *Curr Pharm Biotechnol* 2010; **11:** 69–86.
3 Merabishvili M, Monserez R, van Belleghem J, et al. Stability of bacteriophages in burn wound care products. *PLoS One* 2017; **12:** e0182121.
4 Salmond GP, Fineran PC. A century of the phage: past, present and future. *Nat Rev Microbiol* 2015; **13:** 777–86.

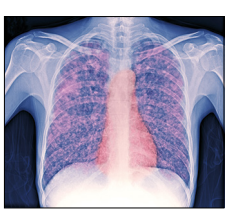
Regimen design and pharmacokinetic–pharmacodynamic science: lessons learned

In *The Lancet Infectious Diseases*, Jung-Kyu Lee and colleagues report a study that substituted ethambutol with linezolid during the intensive phase of treatment for pulmonary drug-susceptible tuberculosis.[1] They randomly assigned patients into three groups: standard treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol, or linezolid (instead of ethambutol) at a dose of 600 mg/day for 2 or 4 weeks. The primary endpoint (ie, culture conversion at 8 weeks of treatment) showed no benefit of linezolid over the control.

Shortening tuberculosis therapy is the primary goal of improving tuberculosis treatment, requiring at least one bactericidal and sterilising drug protected by accompanying drugs to prevent acquired drug resistance.[2,3] Gillespie and colleagues previously evaluated whether ethambutol or isoniazid replaced by moxifloxacin in the intensive phase could shorten treatment duration to 4 months. Unfortunately, despite a more rapid decline in bacterial load, non-inferiority for the two moxifloxacin based regimens was not shown.[4] Absence of penetration of moxifloxacin in cavities and pharmacokinetic–pharmacodynamic science might explain the negative outcome of the study.[5,6]

Compared with moxifloxacin, the early bactericidal activity of linezolid is low,[7] making it less likely that using this drug during the intensive phase for 2 weeks or 4 weeks will be of additional value. Although linezolid potentially possesses sterilising effects,[8] the short period of its use, in the presence of rifampicin makes it unlikely to be effective in this short period of time. As the authors rightly mention, the drug–drug interaction with rifampicin reducing the exposure of linezolid, and the lack of drug exposure measurements make it difficult to estimate whether optimal pharmacokinetic and pharmacodynamic targets were reached. Possibly rifampicin and its enzymatic induction reaching a maximum after approximately 2 weeks might explain the lack of difference in response between 2 and 4 weeks of linezolid. Probably after 2 weeks of linezolid, the linezolid levels fall below a certain threshold, which might result in a static instead of a bactericidal effect. Pharmacokinetic assessment at 2 and 4 weeks during the study could have answered this question.

Determining the dose of linezolid for the treatment of drug-susceptible tuberculosis is challenging, as the majority of evidence on its use is derived from multidrug-resistant-tuberculosis cohorts lacking concomitant use of rifampicin and often also isoniazid. Linezolid drug safety was a serious concern; the authors applied caution when dosing and setting the duration of linezolid use.[9] Concerning the dose, the expected exposure is likely to be sufficient to achieve the target area under the concentration–time curve to minimal inhibitory concentration ratio because the expected linezolid minimal inhibitory concentrations in drug susceptible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See Articles page 46