**Supplementary file three: phage therapy for the treatment of burn wound infections**

| Report details | | Clinical details | | | | Efficacy | | | | Safety & adverse effects |
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| **Author (year), [citation], location, study type** | **No. of relevant reports and microbiology** | **Condition details** | **Phage sensitivity** | **Phage treatment** | **Treatment schedule and route(s)** | **Outcome** | **Cured** | **Improved** | **No response** | |
| Abul-Hassan *et al.* (1990), [35], cited in [34]<br><br>Egypt<br><br>Case series | 30/30<br><br>*Pseudomonas* infection of burn wounds, resistant to all available antibiotics and chemotherapeutic agents. | 6/30 patients were children aged <9, the rest were aged 18-54. Burn wound infection area ranged from 10-21% of body surface area. | Sensitivity confirmed. | *Pseudomonas* phage at $10^{10}$PFU/ml. No further details. | Gauze soaked in phage was applied 3 times daily for 5-17 days as required. Use of concurrent antibiotic therapy unclear. | After phage therapy, 12/30 had negative microbiology; 15/30 had improved, 9/30 had slight improvement and 6/30 had no improvement; discharge stopped in 12/30, diminished in 12/30 and didn't change in 6/30; the effect of phage therapy on skin graft taking was excellent in 6/30, good in 12/30 and poor in 12/30. | 0 | 24 | 6 | No comment. |
| Weber-Dabrowska, Mulczyk & Górski (2000), [47]<br><br>Poland<br><br>Case series | 49/1307<br><br>Infected with *S. aureus, E. coli, Klebsiella, Proteus* or *Pseudomonas.* | Pyogenic burns. Most were chronic infections that had failed antibiotic therapy. | Combined sensitivity data presented for all 1307 patients. | Crude, sterile, bacteriophage lysate. | Three times daily. Adults 10ml, children 5ml.<br><br>Orally and '30 minutes before eating, after neutralisation of the gastric juice'<br><br>Local administration also used on a case-by-case basis, details unclear.<br><br>Therapy duration for all 1307 patients reported as ranging from 1-12 weeks, with an average of 32 days. | 42/49 recovered fully.<br><br>7/49 had 'marked improvement' but bacteria were still detectable. | 42 | 7 | 0 | No comment. |
| Lazareva *et al.* (2001), [37], cited in [34] | 54/54<br><br>Organisms: *Enterococci*, *E. coli, P. aeruginosa* | Burn wound infection. | No phage sensitivity testing reported. | 'Pyophage' cocktail. | Oral therapy. '2 tablets 3 times a day in 1-1.5h before meals' for 7 days. 45 patients treated with antibiotics and phage. Nine treated with phage only. | For patients treated with antibiotics and phage the number of microbial isolates in wounds dropped by 2.2x and positive blood culture | Data unclear. | | | No comment. |

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| Russia<br><br>Case series | and *Staphylococci*. | | | | | results dropped 55 to 37%. Wound healing in 9/9 patients treated with phage only. | 9 | 0 | 0 | |
| Jikia *et al.* (2005), [49]<br><br>Georgia<br><br>Case series | 2/3<br><br>*S. aureus* isolated from burns. | Two males aged 45 and 52 with radiation burns infected with *S. aureus*<br><br>Previous treatment with intravenous antibiotics and antimicrobial ointments for 23 days was unable to resolve the infections. | Sensitivity confirmed. | 'Phagobioderm'. A biodegradable bandage containing a mix of chemotherapeutics and phages:<br><br>$10^6$ PFU/ml 'Pyo' phage cocktail (vs. *S. aureus, P. aeruginosa, E. coli, Streptococcus* and *Proteus*)<br><br>Also: ciprofloxacin ($0.6mg/cm^2$); benzocaine ($0.9mg/cm^2$); α-chymotrypsin ($0.05mg/cm^2$); sodium bicarbonate ($3.75mg/cm^2$) | A single application of 'Phagobioderm' immobilised with sterile bandages<br><br>Wounds examined daily for 5 days and once every 2-4 days thereafter. Microbiology monitored, frequency not reported. | Two days after application of Phagobioderm purulent discharge from both patients reduced to 'almost none'.<br><br>On day 7 both ulcers tested negative for *S. aureus* and both were able to receive skin grafts.<br><br>The *S. aureus* isolates from both patients were later shown to be resistant to ciprofloxacin. | 2 | 0 | 0 | No comment. |
| Marza, Soothill, Boydell & Collyns (2006), [50]<br><br>UK<br><br>Case report | 1/2<br><br>*P. aeruginosa* infection. | 50% surface area burns with skin grafts applied. Refractory to appropriate antibiotic treatment. | Sensitivity confirmed. | Pseudomonas phage at $10^{15}$ PFU/ml. | $10^3$ PFU of phage in 0.2ml was absorbed into two 25mm sterile filter paper discs which were placed on the infected areas.<br><br>After 48h the discs contained $4.3 \times 10^4$ and $1.2 \times 10^6$ PFU respectively, showing phage replication. | *Pseudomonas* was not isolated from the wound 3 days after treatment and subsequent extensive skin grafting was successful. | 1 | 0 | 0 | 'No toxicity to human keratinocytes was observed when they were cultured with the purified phage suspension.'<br><br>'Several hours [after application to the whole wound] the patient had a |

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| | | | | | Phage was then applied to the whole wound area.<br><br>Phage was used alongside IV ceftazidime. | | | | | febrile episode, but similar episodes had occurred previously and otherwise no adverse effects were observed.' |
| Southwest Regional Wound Care Centre, 2006, [31]<br><br>US<br><br>Case series | 1/28<br><br>MRSA positive infected burn wound. | MRSA positive burn wound of approx. 2 months duration in a 60-year-old male on methotrexate and high-dose prednisone for autoimmunity. | No phage sensitivity testing reported. | No details. | Wound debrided and phages applied weekly as part of wound care. | Complete healing in 11 weeks. | 1 | 0 | 0 | No comment. |
| Rose *et al.* (2014), [52]<br><br>Belgium<br><br>Case series | 9/9<br><br>Multi-drug resistant *P. aeruginosa* and/or *S. aureus* infection. | Burn-wound infection. One patient had two burn wound infections.<br><br>Mean patient age was 61 years old (range, 27-88 years old). Mean total burned surface area was 30% (range, 6-45%). | Sensitivity confirmed. | 'BFC-1' cocktail, containing lytic phages active against *P. aeruginosa* (14/1 and PNM) and *S. aureus* (ISP), each at $10^9$ PFU/ml. | BFC-1 was applied in a single topical dose at an average of 0.03ml per $cm^2$.<br><br>The cocktail was applied to half of a patient's wound area, the other half of the wound received standard care. Punch biopsies of each half of the wounds were taken before and 2-4h after BFC-1 therapy. Five phage applications took place during surgery, prior to which wounds had been cleansed with 5% Hibitane and filtered water. Average area of phage administration was 95$cm^2$ (range, 25-150$cm^2$).<br><br>Patients with *P. aeruginosa* were also treated with one dose (25mg/kg initially) of amikacin in combination with ceftazidime (1g initially) or meropenem (2g/8h). Patients with *S. aureus* infection were also treated with vancomycin (1g initially) or linezolid (1200mg/day). | The bacterial loads were found to be very low in 8/10 wounds, owing to delays in admission to the trial during which patients received intensive antibiotic therapy.<br><br>In all cases, the biopsy bacterial load was unchanged after phage application.<br><br>The authors note that they did 'not [expect] that a one-off application […] on a small wound surface would generate conclusive proof of the efficacy'. | 0 | 0 | 9 | 'No adverse effects, clinical abnormalities or changes in laboratory results that could be related to the application of phages were observed.' |

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| Jault *et al.* (2019), [12]<br><br>France & Belgium<br><br>Clinical trial | 10/12<br><br>Two did not receive a full course.<br><br>*P. aeruginosa* infected burns. | Average patient age was 61, with an average of 19% of body surface area burned, with an average of 6% third degree burns. Two patients were receiving antibiotic therapy at the time on enrolment. | Sensitivity confirmed.<br><br>Amongst those who did not reach the primary endpoint 3/10 had resistant colonies. | PP1131 cocktail (12 lytic phages)<br><br>Planned $10^6$ PFU/ml, but deteriorated to $10^2$ PFU/ml (considered subtherapeutic). | Once daily topical application for 7 days. Adjunctive antibiotic therapy at the discretion of the treating physician according to French Burn society recommendations. | Primary outcome was time taken for a sustained reduction in bacterial burden of two quadrants or more assessed by semi-quantitative culture results:<br><br>Phage group: median 144h (95% CI, 48h to not reached)<br><br>Control group: 47h (95% CI, 23-122h) | 0 | 0 | 10 | 'Safety assessments included frequency, duration and severity of adverse events, clinical laboratory tests, vital sign measurements, physical examinations and clinical assessment of burn wounds.'<br><br>'Adverse events' reported among 23% of phage patients and 54% of control patients. No substantial difference between the groups.<br><br>Although the phage titre was $10^2$ PFU/ml, the equivalent of $10^6$ phage particles (most inactive) were applied to patients and 'did not provoke safety issues'. |