Selection and local application of a cocktail of bacteriophages in addition with local colistin therapy and off-label use of ceftolozane/tazobactam for the treatment of a complex bone and joint infection due to multidrug-resistant *P. aeruginosa*

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### Aim
To describe the strategy based on local application of a selected cocktail of bacteriophages in a patient with a complex bone and joint infection (BJI) due to multidrug-resistant *P. aeruginosa*, also managed with local application of colimycin and off-label use of ceftolozane/tazobactam.

### Method
A 62-years-old man with disseminated cancer received radiotherapy followed by cimentoplasty for bone metastases located on right sacroiliac joint. Two months later, a fistula occurred, with clinical evidence of infection requiring cement explantation. The patient still had fever with purulent local discharge. A surgical bone biopsy revealed infection with extensively drug resistant *P. aeruginosa*, only susceptible to colistin and ceftolozane/tazobactam, a new antibiotic not yet indicated for BJI. We proposed a two-stage surgical approach combined with several innovations to maximize a quick healing: local application of a selected cocktail of bacteriophages, local colistin therapy and systemic ceftolozane/tazobactam. Following discussions with the French National Agency for Medicines and Health Products Safety (ANSM), bacteriophages were selected among the anti-Pa bacteriophage library of Pherecydes Pharma. The selection was based on a susceptibility test (phagogram) performed on the patient strain. The four most active bacteriophages were chosen and then manufactured by Pherecydes, outside of a GMP-structure but in accordance to the GMP guidelines. A particular negative-pressure wound therapy (NPWT) system was used to administrated locally 36 MUI/day of colimycin, corresponding to 1200mg of colistin base activity. Twelve cycles/day were scheduled as following: instillation 5min, break 20min, negative pressure 95min. Cefotolozane/tazobactam was prescribed intravenously (1g/500mg/8h).

### Results
During surgery, debridement of the infected bone was performed, and local application of the bacteriophages was done after magistral preparation by the hospital pharmacy. After 4 hours of ventral decubitus, NPWT with administration of colimycin has been set up during 2 weeks. Three other local applications of bacteriophages were done at day 3, 6 and 9. At the time of surgical reconstruction at day 14, the macroscopic aspect was favorable and skin and soft tissue flap was performed. We planned to continue only ceftolozane/tazobactam for another 4 weeks. Cicatrization was rapidly acquired. Unfortunately, the patient developed significant progression of the spine metastases, leading to compression. As a consequence, immunotherapy for the cancer was not performed and the patient died at day 45.

### Conclusion
Management of complex BJI could require multiple innovations such as local application of selected bacteriophages that could be applied during the surgery. This strategy strongly contributed to a rapid healing in the present case.

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