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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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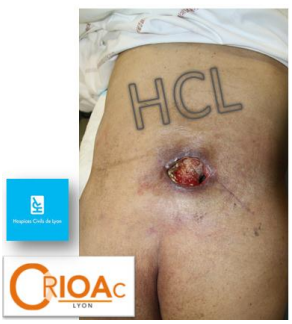
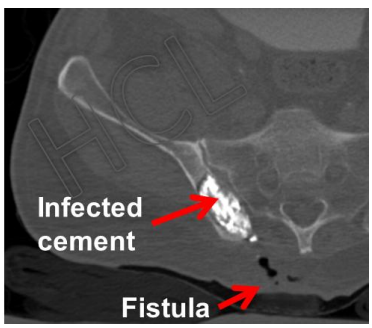
Aim

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 sacro-ilac 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 colistine 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. Ceftolozane/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. Cicatrisation 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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Lyon BJI Study group

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