CLINICAL CASE REPORT

Successful use of bacteriophage therapy for a *Staphylococcus aureus* prosthetic joint infection in Canada

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BACKGROUND: Prosthetic joint infections (PJIs) pose a significant treatment challenge due to biofilm-associated resistance, which limits antibiotic effectiveness. Bacteriophages, naturally occurring viruses that selectively infect and lyse bacteria, can disrupt biofilms, potentially enhancing antibiotic activity. We present the case of a male in his 70s with a history of total hip arthroplasty in 1973 who developed a chronic methicillin-susceptible *Staphylococcus aureus* (MSSA) PJI. Despite eight surgical interventions and multiple courses of suppressive antibiotics, the infection persisted, necessitating the use of bacteriophage therapy.

METHODS: The patient's MSSA isolate was sent to a bacteriophage laboratory in Quebec, who identified effective bacteriophages, and a two-bacteriophage cocktail was selected. Following approval by Health Canada and the University of Calgary (REB23-1733), bacteriophages were administered during a planned incision and drainage (I&D). Locally, bacteriophage was applied topically into the hip, followed by 2 weeks of twice-daily intravenous bacteriophage therapy with standard-of-care intravenous antibiotics.

RESULTS: Therapy was well tolerated except for initial mild rigors. Now, 24 weeks after bacteriophage administration, there is cessation of pain, normalization of inflammatory markers, and significant improvement in quality of life while continuing on suppressive antibiotics.

CONCLUSION: Bacteriophage therapy was safe in our case, and emerging evidence is promising for its use in PJIs. However, regulatory hurdles, cost, and lack of standardized protocols currently limit its use. Classified as experimental therapy in Canada, bacteriophage use is restricted to clinical trials. This case underscores the potential for broader adoption of bacteriophage therapy in managing PJIs across Canada.

KEYWORDS: antibiotic, infection, joint, phage, prosthetic joint infection, therapy

HISTORIQUE : Les infections des prothèses articulaires (IPA) sont très difficiles à traiter en raison de la résistance associée au biofilm qui limite l'efficacité antibiotique. Les bactériophages, des virus naturels qui infectent et lysent sélectivement les bactéries, peuvent perturber les biofilms et peut-être améliorer l'activité antibiotique. Les chercheurs présentent le cas d'un septuagénaire qui a subi une arthroplastie totale de la hanche en 1973 et qui a contracté une IPA chronique par *Staphylococcus aureus* résistant à

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la méthicilline (SARM). Malgré huit interventions chirurgicales et de multiples traitements d'antibiotiques suppresseurs, l'infection a persisté et nécessité une phagothérapie.

MÉTHODOLOGIE : L'isolat de SARM prélevé chez le patient a été envoyé à un laboratoire de bactériophages de Québec qui a déterminé les bactériophages efficaces, et un cocktail de deux bactériophages a été sélectionné. Après avoir obtenu l'approbation de Santé Canada et de l'Université de Calgary (REB23-1733), les bactériophages ont été administrés lors d'une incision et d'un drainage planifiés. Le bactériophage a été appliqué localement sur la hanche, puis une phagothérapie a été administrée par voie intraveineuse deux fois par jour pendant deux semaines, combinée aux antibiotiques par voie intraveineuse qui correspondent à la norme de soins.

RÉSULTATS : Le traitement était bien toléré, sauf de légères rigidités initiales. Vingt-quatre semaines après la phagothérapie, la douleur avait cessé, les marqueurs inflammatoires s'étaient normalisés et la qualité de vie du patient, qui continuait de recevoir des antibiotiques suppresseurs, s'était considérablement améliorée.

CONCLUSION : La phagothérapie était sécuritaire dans ce cas, et des données probantes émergentes sont prometteuses pour les utiliser en cas d'IPA. Cependant, les obstacles en matière de réglementation, le coût et l'absence de protocoles standardisés en limitent actuellement l'usage. Classée comme traitement expérimental au Canada, la phagothérapie est restreinte aux études cliniques. Ce cas souligne le potentiel d'adopter la phagothérapie plus largement pour prendre en charge de l'IPA au Canada.

MOTS-CLÉS : antibiotiques, articulation, infection, infection de l'articulation prothétique, phage, thérapie

LAY SUMMARY

Artificial joint infections are serious complications that can occur after joint replacement surgery. These infections are particularly difficult to treat because bacteria form protective slime layers on the hardware called *biofilms*, making them resistant to antibiotics. In many cases, removing and replacing the joint hardware is the only way to cure the infection. However, for some patients, another joint surgery is impossible due to medical risks or bone damage, leaving amputation as the last option.

This case report describes the first published use of bacteriophage therapy for a *Staphylococcus aureus* prosthetic joint infection in Canada. *Bacteriophages*, or *phages*, are viruses that specifically attack and kill bacteria while leaving the human host unharmed. Previously used before the development of antibiotics, bacteriophages are now emerging as a promising option for combating increasingly common antibiotic-resistant infections.

The patient, a male in his 70s, had suffered from a chronic *Staphylococcus aureus* bacterial infection in his replaced hip joint for over a decade. Traditional treatments, including multiple surgeries and long-term antibiotics, failed to cure the infection. He continued to live with persistent pain, inability to walk without a walker, and depression. Since the only remaining surgical option was a high-risk amputation, experimental bacteriophage therapy was pursued. The patient's bacteria were tested to find matching bacteriophages, and the treatment was approved.

Bacteriophages were delivered directly into the infected joint during surgery and intravenously afterwards, alongside traditional antibiotics. The treatment was well tolerated, with only mild side effects; 6 months after therapy, the patient reported no pain, improved mobility with a single cane, and no signs of infection.

Although more research is needed, this case highlights bacteriophage therapy's potential as a life-changing treatment for severe infections. It also underscores the need for better access to bacteriophage therapy in Canada, where it remains experimental and difficult to obtain.

CASE

We present a case of a male patient in his 70s with remote right hip injury five decades prior that was complicated by avascular necrosis necessitating a total hip arthroplasty. The patient had post-operative complications including loosening of the acetabular component, which required multiple revisions such as placement of an anterior inferior iliac spine plate and screws along with cerclage wires around the femur for a peri-prosthesis fracture. Eleven years prior to presentation, following a mild traumatic injury that resulted in a draining hematoma, the patient developed a prosthetic joint infection (PJI) caused by methicillin-susceptible *Staphylococcus aureus* (MSSA).

The PJI diagnosis was established according to Musculoskeletal Infection Society (MSIS) criteria, and the infection was managed at the time with incision and drainage (I&D) and 24 weeks of antibiotics, a longer course than the standard 12 weeks, owing to increased risk of infection relapse and multiple drug allergies (Table 1) (1). Hardware removal was not a viable option due to destruction of the underlying bone in the lateral subtrochanteric region, and the infection relapsed, resulting in a draining sinus tract and pain with significant functional limitation (Figure 1).

Table 1: The patient's PJI treatment course. All surgeries were performed on the right hip. MSSA isolates were susceptible to the following antibiotics using Clinical and Laboratory Standards Institute (CLSI) breakpoints unless stated otherwise: cloxacillin, cefazolin, clindamycin, tetracycline, levofloxacin, trimethoprim-sulfamethoxazole, and rifampin. Samples used for intraoperative cultures are a mix of synovial fluid, tissue, and deep wound swabs

Time prior to phage therapy	Procedure	Intraoperative cultures	Treatment
11 years prior	I&D with partial removal of cerclage wire	MSSA in 2/3	• Cloxacillin/rifampin (anaphylaxis) THEN • Daptomycin × 12 weeks THEN • Levofloxacin × 12 weeks
9 years prior	I&D with sequestrectomy and partial removal of hardware	MSSA in 3/3	• Daptomycin THEN • Linezolid × 6 weeks
9 years prior (4 months after previous surgery)	I&D with arthrotomy (planned surgery and not for recurrence of infection)	No growth in 1/1	• Doxycycline and trimethoprim-sulfamethoxazole suppression therapy
8 years prior	I&D with antibiotic bead insertion (vancomycin and tobramycin)	MSSA in 3/5	• Linezolid × 6 weeks THEN • Doxycycline and trimethoprim-sulfamethoxazole suppression therapy
4 years prior	I&D with sequestrectomy	MSSA in 5/5 Susceptible by Kirby-Bauer disk diffusion to: • Clindamycin (31 mm) • Erythromycin (31 mm) • Cefoxitin (37 mm), oxacillin and cefazolin (inferred susceptible from cefoxitin) • Trimethoprim-sulfamethoxazole (20 mm) • Ciprofloxacin (22 mm) • Levofloxacin (26 mm) • Rifampin (40 mm) • Tetracycline (29 mm)	• Linezolid × 6 weeks THEN • Doxycycline and trimethoprim-sulfamethoxazole suppression therapy
1 year prior	I&D with femoral osteotomy	Small-colony variant *S. aureus* in 3/5 (susceptibility testing was not performed by the laboratory as it was felt it would be unreliable)	• Cefadroxil and trimethoprim-sulfamethoxazole suppression therapy
Day of phage therapy	I&D with sequestrectomy	MSSA (resistant to trimethoprim-sulfamethoxazole) in 3/4	• Intraoperative bacteriophage (× 1) AND • Intravenous bacteriophage BID × 14 days AND • Cefazolin and doxycycline × 6 weeks THEN • Doxycycline and cefadroxil × 6 months (minimum)

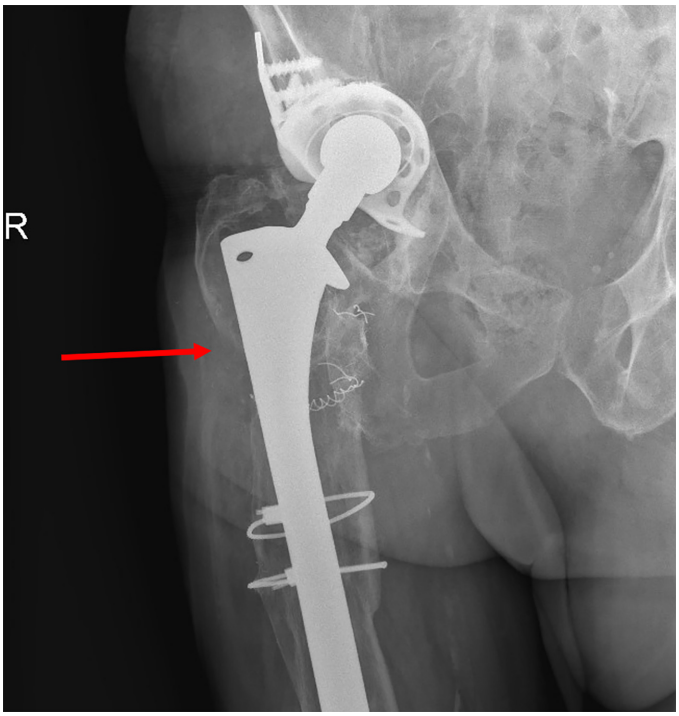

Figure 1: Pre-surgical x-ray of the right pelvis prior to bacteriophage administration. Note the extent of hardware in place and the loss of bone in the lateral subtrochanteric region *(arrow)*

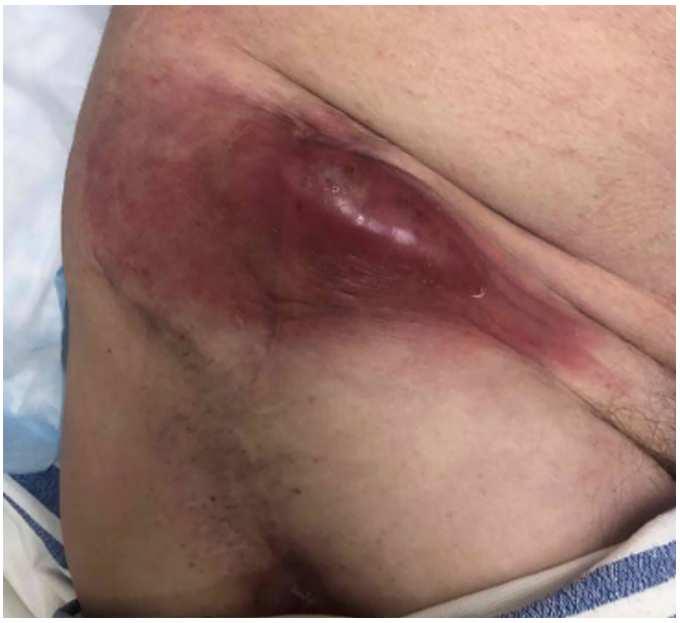

Figure 2: The patient had a clinical breakthrough 1 month prior to bacteriophage administration, with a draining sinus tract overlying the acetabular hardware despite adherence to two oral antibiotics: trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline (both were active against the patient's *S. aureus* isolate)

Subsequently, the patient has had seven I&D procedures with tissue debridement on the hip from relapsed MSSA PJIs necessitating multiple courses of both parenteral and oral antibiotics (Table 1) with near continuous use for the past decade.

Treatment options were limited by multiple drug intolerances and allergies including anaphylaxis with cloxacillin, rifampin, and vancomycin; urticaria with daptomycin and clindamycin; and Stevens-Johnson syndrome with levofloxacin. The infection relapsed despite sequential courses of monotherapy with agents active against the patient's *S. aureus* isolate (cefadroxil, trimethoprim-sulfamethoxazole [TMP-SMX], and doxycycline), prompting escalation to dual oral therapy with highly bioavailable agents (TMP-SMX plus doxycycline) as salvage therapy (Figure 2). In discussion with orthopaedic surgery, it was determined that the only definitive management for his infection would be a highly morbid right hemipelvectomy. After the patient's I&D 1 year prior, we began to explore the possibility of bacteriophage therapy.

At a Quebec laboratory, bacteriophages that were active against the patient's most recent *S. aureus* isolate were identified. Phages were produced under BSL-2 conditions using closed, sterilizable fermentation systems, with controlled inoculation of host bacteria followed by phage infection with monitored lysis. Cultures were clarified by filtration, with all handling performed aseptically in validated closed systems. Clarified lysates underwent concentration, diafiltration, and endotoxin removal, followed by sterile filtration and quality testing. Final phage preparations were stored at 2° C to 8° C in validated buffers to maintain stability and viability. For safety, bacteriophage solutions are screened for endotoxins, and the genomes are screened for toxicity determinants, virulence determinants, and antibiotic-resistance determinants. Detailed upstream and downstream process steps, critical in-process controls, and equipment qualification records are provided under Supplemental Material.

Lytic activity was tested *in vitro* with killing assays against the patient's isolate (Figure 3). Bacteriophage-antibiotic synergy testing with individual antibiotics identified cefazolin as showing the greatest synergistic activity, with no antagonism observed. Upon identifying active bacteriophages, a two-phage cocktail was selected after expert consultation (Dr. G. Suh). This approach was chosen to provide sufficient coverage against the patient's *S. aureus* isolate while limiting manufacturing complexity, minimizing endotoxin exposure, and avoiding potential antagonism among additional phages.

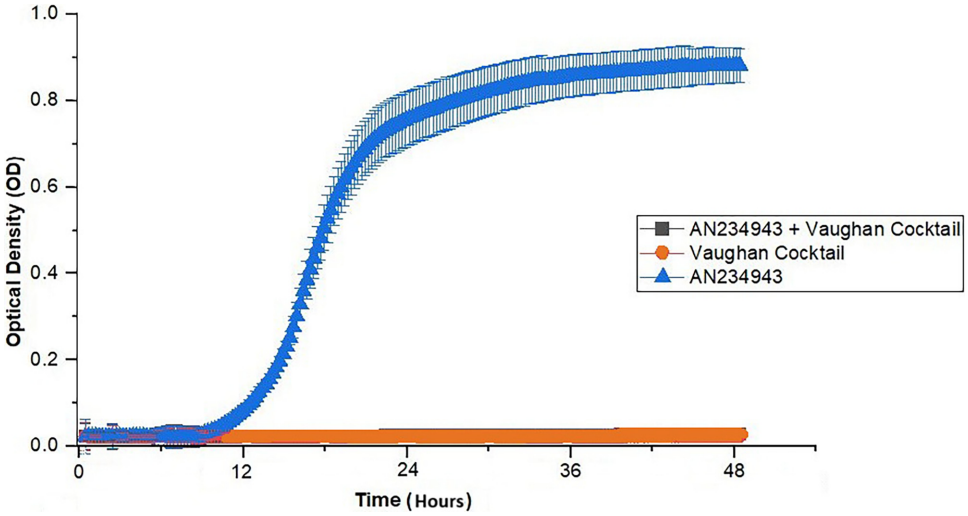

Figure 3: Bacterial growth kinetics (mean ± SD) in three independent bacteriophage assays: MSSA isolate AN234943 *(blue)*, MSSA isolate with Vaughan (named for treating physician) anti–*S. aureus* bacteriophage cocktail *(grey)*, and bacteriophage cocktail alone *(red)*, measured by optical density 600 nm every 15 minutes

Bacteriophages are an experimental therapy in Canada, therefore approval for a single-patient trial (open-label individual patient) was needed from Health Canada and the University of Calgary (REB23-1733). Planned outcomes were: (1) clinical response, defined as absence of wound drainage, swelling, erythema, pain, or fever, together with EQ-5D questionnaire results; (2) biochemical response, defined as normalization of white blood cell count and C-reactive protein; and (3) safety, defined as documentation of any adverse effects (protocol available in Supplemental Material). Study design was based on the STAMP protocol (2), and the trial was also registered on clinicaltrials.gov (NCT06456424).

The patient went for planned surgical debridement with bacteriophage administration. Devitalized tissue was removed, the sinus tract was excised, and three areas of purulence were irrigated and debrided. Intraoperatively, 10^9 plaque-forming units (PFU) of the 1 mL bacteriophage cocktail was administered locally (diluted into 20 mL of sterile saline to increase volume) with one-half administered around the acetabulum and the other half around the cerclage wires of the exposed femoral stem. Cefazolin was administered concurrently. The procedure was well tolerated with no systemic inflammatory response syndrome–like reaction. The patient then received 10^9 PFU of intravenous bacteriophage twice daily for a 2-week course. Treatment was initiated in the inpatient setting and, following discharge, was maintained through our outpatient Home Parenteral Therapy Program (HPTP). Here, nursing staff infused the bacteriophage therapy twice daily with clinical assessments before and after each administration. The first two intravenous bacteriophage infusions were associated with mild rigors lasting around 20 minutes, without hypotension, toward the end of administration. These were subsequently prevented with premedication using diphenhydramine 50 mg orally and cetirizine 10 mg orally given 1 hour before each infusion. Blood work was done on days 0, 4, 8, 15, 29, as well as weeks 12 and 24 to monitor for adverse events (Table 2). Bacteriophage was given for 2 weeks in addition to intravenous cefazolin and oral doxycycline for 6 weeks, followed by oral cefadroxil and doxycycline to be continued for a minimum of 6 months, with the expectation of lifelong therapy. The antibiotic combination was selected based on prior tolerance and concern for breakthrough infection.

24 weeks after completion of the bacteriophage therapy, the patient has had remarkable improvements and no longer meets criteria for having a PJI (1). Pain in the right hip is no longer present (8/10 pre-operative decreased to 0/10), inflammatory markers have normalized (Table 2), the patient has not required another arthrocentesis, and there has been no recurrence of sinus tract formation, which previously presented 2 to 3 months after surgery. The patient endorses significant improvement in quality of life with the ability to ambulate up to 5,000 steps per day (pre-operative 1,250 steps/day), and he no longer requires a 2-wheeled walker and uses a single cane for long walks with no support device for short walks. His sleep requirements have decreased from 18 hours/day (pre-operative) to 8 hours/day, and quality of life as measured by EQ-5D has increased from 4/100 to

Table 2: The patient's laboratory investigations at the start of, during, and after treatment. WBC = white blood cells, ALT = alanine transaminase, ALP = alkaline phosphatase, CRP = C-reactive protein

	Reference	Day 0	Day 4	Day 8	Day 15	Day 29	Week 12	Week 24
Hemoglobin (g/L)	135–175	144	128	127	127	137	142	144
WBC (10^9/L)	4.0–11.0	8.0	7.6	9.4	7.4	7.8	10.8	6.8
Platelets (10^9/L)	140–400	354	267	318	255	275	371	233
Creatinine (μmol/L)	50–120	60	60	48	43	52	57	52
ALT (U/L)	<70	8	9	N/A	5	8	16	14
ALP (U/L)	40–120	N/A	74	78	80	97	94	N/A
Total bilirubin (μmol/L)	<20	N/A	3	4	4	7	2	N/A
CRP (mg/L)	<10.0	55.3	40.8	32.5	16	11.8	36.4	6.3

88/100 (3). The patient was able to ride his motorcycle for the first time in 5 years. Routine follow-up is planned for a minimum of 12 months to ensure a lasting effect (absence of recurrent sinus tract or systemic signs of infection) of the bacteriophage therapy.

DISCUSSION

PJIs pose a significant therapeutic challenge as optimal management of chronic infections typically requires a combination of antibiotic therapy and removal of all affected prosthetic material, most commonly through one- or two-stage revision, although other surgical strategies may be considered in selected cases. However, this is often not feasible due to patient comorbidities or fragility of the underlying bone (4). In cases in which hardware cannot be removed, outcomes are poor. A recent systematic review estimated a recurrence rate of 35.9% (95% CI: 23.9% to 48.0%) among patients with hip and knee PJIs managed with implant retention (5). Rates vary depending on the infecting organism, the type of surgical management, and patient comorbidities; many such patients ultimately require lifelong suppressive therapy. Outcomes are particularly unfavourable in *S. aureus* PJIs, with one large cohort study reporting failure rates as high as 45% (6).

The high relapse rates of PJIs are thought to be primarily due to biofilm formation. Biofilms are structured communities of bacteria, such as *S. aureus*, that are encased in an extracellular polymeric substance (EPS) matrix that adheres to the surfaces of prosthetic material. Beyond serving as a physical barrier, bacteria within biofilms often shift into a stationary growth phase, making them less susceptible to antibiotics that target actively dividing cells (7).

Bacteriophages, or phages, are naturally occurring viruses that specifically infect and lyse bacteria. First discovered in the early 20th century by Felix d'Herelle, a French-Canadian microbiologist, bacteriophage therapy fell out of popularity with the advent of antibiotics in the 1940s (8). In recent years, with the alarming increase in antibiotic-resistant bacteria, bacteriophage therapy has experienced a renaissance. Although antibiotics remain the mainstay of therapy for bacterial infections, the challenges of antimicrobial resistance and increasing patient complexity have prompted researchers to explore bacteriophage therapy as a potential complementary strategy.

Bacteriophages may offer unique advantages in the treatment of biofilms by directly penetrating and targeting embedded bacteria. Some bacteriophages produce depolymerases and nucleases that enzymatically degrade the EPS matrix, disrupting biofilm structure while simultaneously infecting and lysing bacteria (7). Once a bacterium is infected, it functions as a factory and produces numerous progeny bacteriophages that are released upon lysis, thereby exponentially amplifying bacteriophage concentrations at the site of infection (9). Biofilm disruption also exposes bacteria to host immune defenses and enhances the activity of concurrent antibiotics (7).

Bacteriophage therapy represents a step towards personalized medicine within infectious diseases, offering specificity against pathogenic bacteria while sparing the normal microbiota. It has been used in respiratory, urological, musculoskeletal, and cardiac infections, among others (10). Published data on bacteriophage therapy in Canada is scant, however through personal correspondence we know of at least three previously treated Canadian patients, including a PJI and another urinary tract infection (11,12).

Evidence for bacteriophage therapy in PJIs is still emerging and at present is mainly limited to case series and reports. To date, only a single clinical trial has been published. A 2023 study enrolled 23 patients to treatment to bacteriophage therapy and matched them according to surgical intervention to 22 historical controls, with both

groups receiving standard-of-care antibiotic therapy. Bacteriophage concentrations of at least 10^5 PFU/mL were mixed into bone cement during one-stage revisions and then injected daily into the joint through a peri-prosthetic drain for up to 10 days. With this, the relapse rate of the bacteriophage group was 8 times lower than the controls (4.5% vs 36.4%). Among those who received bacteriophage therapy, the pathogens were mainly *Staphylococcus* spp., with *Staphylococcus epidermidis* ($n = 14$) and *S. aureus* ($n = 9$) (13).

Following this, a 2023 systematic review assessed 33 bone and joint infections, comprising 10 cases of osteomyelitis and 20 PJIs (including the aforementioned study) (14). The main pathogens involved were *S. aureus* ($n = 13$), *Pseudomonas aeruginosa* ($n = 10$), *S. epidermidis* ($n = 3$), *Klebsiella pneumoniae* ($n = 3$), *Enterococcus faecalis* ($n = 3$), and polymicrobial ($n = 5$). In almost all cases, the patients had significant bone loss (as in our case) and were non-operable for hardware removal. There is no consensus for bacteriophage concentration, route, or duration. Most patients ($n = 28$) received direct application of bacteriophage (ie, intra-articular injection or topical application during I&D), whereas 4 had just intravenous administration and 13 received a combination of direct application and intravenous injection. One patient received oral bacteriophage (with clinical cure). Dosing varied with a range of 10^7 to 10^{11} PFU, durations of 1 to 7 weeks, and frequencies of weekly to 3×/day. Despite the varied protocols, microbiologic or clinical success occurred in 29/33 (88%), and of the 19 successful PJI cases, 10 were surgically managed with debridement, antibiotics, and implant retention (DAIR).

A recent retrospective case series of 100 patients from Belgium had similar results, with 77.2% of patients having clinical improvement and 61.3% having eradication of target bacteria (15). There was significant heterogeneity in the source of the clinical infection, with only 14% representing bone infections, and the microbiology included *Pseudomonas aeruginosa* (49%) and *Staphylococcus aureus* (39%) as being the most common bacteria targeted.

A commonly cited reason for the low adoption of bacteriophage therapy is the perceived risk of adverse effects including immune reactions to the bacteriophages, bacterial endotoxin release, and contamination during the manufacturing process. Endotoxins and other contaminants are screened for during the manufacturing process, and although antibodies to bacteriophages do develop within days, they do not seem to cause harm to patients, and their impact on clinical efficacy is unknown (16). Clinical data support a favourable safety profile; prospective studies in *S. aureus* infections have demonstrated that bacteriophage therapy is safe (17), and a systematic review found that adverse effects occurred in 7% of cases, less than the 15% in control patients (10). Transient transaminitis is the most common adverse effect, followed by a transient inflammatory response to bacterial cells/cell fragments, often manifested as fevers and chills (14,18).

Although the future of bacteriophage therapy is promising, there are still many challenges that need to be overcome. Despite reports of efficacy and safety, bacteriophage therapy remains inaccessible for most patients with intractable infections. Personalised therapy is increasingly used for other chronic conditions such as chimeric antigen receptor (CAR) T-cell therapy in cancer, opening the possibility of expanded use of patient-specific therapy for infections. Currently, identifying a bacteriophage match and preparing and administering the bacteriophage cocktail can only be done with support of research funding, which prevents it from being a readily accessible option. Aside from cost, regulatory hurdles are burdensome to overcome, with one case series having a median number of 170 days until administration, which was similar to our Canadian experience (19). Currently, there are no bacteriophage preparations approved by Health Canada, and administration within Canada is restricted to research settings through clinical trials. There is need for standardization in bacteriophage production, dosing, route of administration, duration of therapy, and how both efficacy and adverse effects are reported.

In May 2025, the World Health Organization Regional Office for Europe published "Building the Evidence for the Use of Bacteriophage Therapy," a document highlighting bacteriophages as promising precise treatments for antimicrobial resistance across human, animal, and environmental sectors and calling for a strengthened evidence base (20). To date, there has only been one report of bacteriophage therapy use for a prosthetic joint infection in Canada (11), and we hope that this case will help lead the way for its future use in difficult-to-treat infections.

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ETHICS APPROVAL: University of Calgary REB23-1733

INFORMED CONSENT: The authors have obtained patient consent for all details used in this case report.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL: ClinicalTrials.gov ID NCT06456424; Health Canada (NOL) No Objection Letter: Vaughan-AN234943, Control # 286405, concerning Protocol # PHAGE-2024-01, Protocol (OLIP) Version 2.0.

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