

Appendix

Appendix I Search formulae used.

	phage		osteoarticular		infection
PubMed & Cochrane & PHAGE*	phage	AND	osteoarticular	AND	infection
	OR		OR		OR
	bacteriophage		orthopaedic		osteomyelitis
	OR		OR		OR
	phage therapy		orthopedic		septic arthritis
	OR		OR		OR
	"bacteriophages"[MeSH Terms]		musculoskeletal		osteitis
	OR		OR		OR
	"phage therapy"[MeSH Terms]		bone		"infections"[MeSH Terms]
			OR		OR
			joint		"osteomyelitis"[MeSH Terms]
			OR		OR
			prosthetic		"arthritis, infectious"[MeSH Terms]
			OR		OR
			prosthetic joint		"osteitis"[Mesh]
			OR		
		implant			
		OR			
		"orthopedics"[MeSH Terms]			

OR
 "orthopedic procedures"[MeSH Terms]
 OR
 "musculoskeletal system"[Mesh]
 OR
 "bone and bones"[MeSH Terms]
 OR
 "joints"[MeSH Terms]
 OR
 "prostheses and implants"[MeSH Terms]

EMBASE		AND	osteoarticular	AND	infection
	phage				
	OR		OR		OR
	bacteriophage		orthopaedic		osteomyelitis
	OR		OR		OR
	phage therapy		orthopedic		septic arthritis
	OR		OR		OR
	'bacteriophage'/exp		musculoskeletal		osteitis
	OR		OR		OR
	'phage therapy'/exp		bone		'infection'/exp
			OR		OR
			joint		'osteomyelitis'/exp
			OR		OR
			prosthetic		'bacterial arthritis'/exp
			OR		OR
			prosthetic joint		'osteitis'/exp
			OR		

implant

OR

'orthopedics'/exp

OR

'orthopedic surgery'/exp

OR

'musculoskeletal system'/exp

OR

'bone'/exp

OR

'joint'/exp

OR

'prostheses and orthoses'/exp

*MeSH terms were not used to search publications in the journal *PHAGE*.

Supplemental Table 2

Ref.	Year of Publication	Country	Patient number	Gender	Age	Infection site	Orthopaedic diagnosis	Surgery since start of infection history	Bacteria targeted by phage	Phage provenance, composition and susceptibility	Phage administration modality	Phage administration frequency and duration	Concomitant AB	SAT	Outcome (follow-up since end of PT)
Ramirez - Sanchez (26)	2021	USA	P1	F	61	1) Knee	1) Right knee PJI	1) Multiple debridements, two-stage exchange	1) <i>Staphylococcus aureus</i> (MSSA)	1) Biotech (Armata); three phages per bacteria; tested for specificity	1) Topical (IOIA) + IV	1) One intra-articular injection followed by IV injections twice daily for 2 weeks	1) Yes	1) Yes	1) D2
						2) Knee	2) Right knee PJI	2) Two-stage exchange + PT .	1) <i>Staphylococcus aureus</i> (MSSA)	2) Biotech (APT); one phage per bacteria; tested for specificity	2) Topical (IOIA) + IV	2) One intra-operative injection followed by IV injections twice daily for 6 weeks	2) Yes	2) No	(6 months) 2) A (20 months)
Ferry et al. (27)	2021	France	P2	M	88	Knee	Left knee PJI	DAIR, arthroscopic DAIR + PT	<i>Pseudomonas aeruginosa</i>	Biotech (Pherecydes); three phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery	Yes	Yes	E (~12 months)
Doub et al. (24)	2021	USA	P3	F	79	Knee	Left knee PJI (long stem prosthesis)	DAIR, two-stage exchange, DAIR + PT	<i>Staphylococcus epidermidis</i>	In-house/Biotech (Phagomed); one phage per bacteria; tested for specificity	Topical (IOIA)	Once during surgery	Yes	Yes	A (~5 months)
Ferry et al. (28)	2020	France	P4	M	80	Knee	Left knee PJI (long stem prosthesis)	One-stage exchange, DAIR + PT , DAIR	<i>Staphylococcus aureus</i> (MSSA)	Biotech (Pherecydes); three phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery after joint closure	Yes	Yes	B1 (~30 months)
			P5	M	84	Knee	Right knee PJI (long stem prosthesis)	Two-stage exchange, one-stage exchange, DAIR, DAIR + PT	<i>Staphylococcus aureus</i> (MSSA)	Biotech (Pherecydes); three phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery after joint closure	Yes	Yes	A (~7 months)
			P6	F	83	Knee	Right knee PJI (long stem prosthesis)	DAIR, DAIR + PT , DAIR	<i>Staphylococcus aureus</i> (MSSA)	Biotech (Pherecydes); three phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery after joint closure	Yes	Yes	B2 (~11 months)
Nadareishvili et al. (29)	2020	Georgia	P7	M	74	Sternum	Sternum osteomyelitis	None	<i>Staphylococcus aureus</i> (MSSA)	Commercial (GEI); three different phage cocktails; tested for specificity	Topical (sup.) + PO	Daily PO and topical for 20 days, pause for 2 weeks, 2 weeks as first round	No	No	A (~12 months)

	P8	F	60	Tibia	Right tibia chronic osteomyelitis	Reconstructive surgery involving antibiotic cement	<i>Staphylococcus aureus</i> (MSSA)	Commercial (GEI); four different phage cocktails; tested for specificity	Topical (sup.) + PO	Twice daily PO and topical for 20 days, pause for 3 weeks, 15 days PO three times daily and topical two times daily, another 3 week break, another 15 days PO two times daily and topical	No	No	A (~24 months)		
	P9	M	69	Foot	Left foot osteomyelitis	None	<i>Staphylococcus aureus</i> + <i>Enterococcus faecalis</i>	Commercial (GEI); two different phage cocktails; tested for specificity	Topical (sup.) + PO	Twice daily PO and once daily topical for 20 days, pause for 2 weeks, 20 days like first round	No	No	A (~12 months)		
Ferry et al. (30)	2020	France	P10	M	49	Knee	Left knee PJI (megaprosthesis)	Two-stage exchange, DAIR + PT + DIEAP free flap, 2 successive debridements, transfemoral amputation	<i>Staphylococcus aureus</i> (MSSA)	Biotech (Pherecydes); two phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery	Yes	-	E (~12 months)
Cano et al. (31)	2020	USA	P11	M	62	Knee	Right knee PJI	DAIR, two-stage exchange, arthrotomy and synovectomy, one-stage exchange, two-stage exchange, tibial component revision, 3 successive incision and drainages	<i>Klebsiella pneumoniae</i>	Biotech (APT); one phage per bacteria; tested for specificity	IV	Daily IV infusions each weekday for a total of 40 doses	Yes	Yes	A (~8.5 months)
Doub et al. (25)	2020	USA	P12	M	72	Knee	Right knee PJI	DAIR, two-stage revision, 2 successive DAIRs, debridement + prosthesis explantation + spacer implantation + PT , debridement + spacer exchange + PT , cemented femoral megaprosthesis implantation + PT	<i>Staphylococcus aureus</i> (MRSA)	Biotech (APT); one phage per bacteria; tested for specificity	Topical (IOIA) + IV	Once during surgery; three IV infusions; two more times during two separate surgeries	Yes	No	A (-)
Tkhilais hvili et al. (32)	2019	Germany	P13	F	80	Knee + Femur	Right knee PJI and femur chronic osteomyelitis	Prosthesis explantation + distal femur resection + bone spacer implantation, prosthesis reimplantation, prosthesis explantation + debridement + PT + spacer implantation, debridement + spacer exchange, prosthesis reimplantation	<i>Pseudomonas aeruginosa</i>	Institute (GEI); one phage; tested for specificity	Topical (IOIA)	Once during surgery; three times a day for five days via drainage tubes	Yes	No	C1 (~11.5 months)
Onsea et al. (33)	2019	Belgium	P14	-	-	Pelvis	Ilium chronic osteomyelitis	Multiple debridements, removal of osteosynthesis material + PT	<i>Pseudomonas aeruginosa</i> + <i>Staphylococcus epidermidis</i>	Institute (QAMH); phage cocktail; one of two bacteria subject to specificity testing	Topical (IOIA)	Once during surgery via drainage tubes; three times a day for seven days via drainage tubes	Yes	-	A (~16 months)
	P15	-	-	Femur	Femur chronic osteomyelitis	Multiple debridements, removal of osteosynthesis material + PT , bone transport procedure with long-term	<i>Pseudomonas aeruginosa</i> + <i>Staphylococcus epidermidis</i>	Institute (QAMH); phage cocktail; tested for specificity	Topical (IOIA)	Once during surgery via drainage tubes; three times a day for ten days via drainage tubes	Yes	-	C1 (~16 months)		

external fixation															
			P16	-	-	Femur	Femur chronic osteomyelitis	Multiple debridements, removal of osteosynthesis material + PT	<i>Staphylococcus aureus</i>	Institute (QAMH); phage cocktail; tested for specificity	Topical (IOIA)	Once during surgery via drainage tubes; three times a day for nine days via drainage tubes	Yes	-	A (~8 months)
			P17	-	-	Femur	Femur chronic osteomyelitis	Multiple debridements, removal of osteosynthesis material + PT	<i>Enterococcus faecalis</i>	Commercial (GEI); phage cocktail; tested for specificity	Topical (IOIA)	Once during surgery via drainage tubes; three times a day for seven days via drainage tubes	Yes	-	A (~8 months)
Nir-Paz et al. (34)	2019	Israel	P18	M	42	Tibia	Left tibial osteomyelitis	Multiple surgeries including: irrigations and debridements, spacer implantation, secondary bone graft, flap coverage	<i>Acinetobacter baumannii</i> + <i>Klebsiella pneumoniae</i>	Biotech (APT); single phage per bacteria; tested for specificity	IV	Administered over a period of five days followed by a period of six days one week later (unspecified frequency)	Yes	-	A (~8 months)
Patey et al. (35)	2018	France	P19	M	44	-	Multiple fractures (infected)	Yes (no details provided)	<i>Staphylococcus aureus</i>	Commercial; -; tested for specificity	Topical (IOIA)	Administered for several weeks (unspecified frequency)	Yes	-	A (-)
			P20	M	25	Pelvis	Pelvic bone infection	Yes (no details provided)	<i>Staphylococcus aureus</i> + <i>Pseudomonas aeruginosa</i>	Commercial; -; tested for specificity	Topical (IOIA)	Administered in the days following the operation (unspecified frequency)	Yes	-	A (-)
			P21	F	40	Foot	Right foot complex fracture (infected)	Yes (no details provided)	<i>Staphylococcus aureus</i>	Commercial; -; tested for specificity	Topical (IOIA)	Administered in the days following the operation (frequency unspecified)	Yes	-	A (-)
			P22	F	80	Knee	Knee PJI	None	<i>Pseudomonas aeruginosa</i>	Commercial; -; tested for specificity	Topical (IOIA)	-	Yes	-	C2 (-)
			P23	F	61	Jaw	Jaw fracture (infected)	Yes (no details provided)	<i>Staphylococcus aureus (MRSA)</i>	Commercial; -; tested for specificity	Topical (IOIA)	-	Yes	-	A (-)
			P24	F	90	Femur + Hip	Hip PJI (femoral fracture under hip prosthesis infection)	Yes (no details provided)	<i>Staphylococcus aureus (MRSA)</i>	Commercial; -; tested for specificity	Topical (IOIA)	Administered in the 10 days following surgery (unspecified frequency)	Yes	-	A (12 months)
			P25	F	72	Knee	Left knee PJI	Yes (no details provided)	<i>Staphylococcus</i> sp.	Commercial; -; tested for specificity	Topical (IOIA)	-	Yes	-	D2 (-)
			P26	M	84	Tibia	Left tibia osteomyelitis	Yes (no details provided)	<i>Staphylococcus aureus (MRSA)</i>	Commercial; -; tested for specificity	Topical (IOIA)	-	Yes	-	A

														(-)	
			P27	F	68	Tibia	Tibia fracture infection	Yes (no details provided)	<i>Staphylococcus aureus</i>	Commercial; -: tested for specificity	Topical (IOIA)	-	Yes	-	C1
(-)															
Ferry et al. (36)	2018	France	P28	F	80	Hip	Right hip PJI	DAIR, one-stage exchange, two-stage exchange, 2 successive DAIRs, DAIR + PT, DAIR	<i>Pseudomonas aeruginosa</i> + <i>Staphylococcus aureus</i> (MSSA)	Biotech (Pherecydes); three phages per bacteria; one of two bacteria subject to specificity testing	Topical (IOIA)	Once during surgery	Yes	Yes	C1 (~18 months)
Fish et al. (37)	2018	USA	P29	F	63	Toe	Right second toe distal phalangeal osteomyelitis	None	<i>Staphylococcus aureus</i> (MSSA)	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	One injection into surrounding soft tissues weekly for seven weeks	Yes	No	A (~35 months)
Ferry et al. (38)	2018	France	P30	M	~60	Pelvis	Ilium chronic osteomyelitis	Debridement, debridement + PT, muscle flap reconstruction	<i>Pseudomonas aeruginosa</i>	Biotech (Pherecydes); four phages per bacteria; tested for specificity	Topical (IOIA)	Once during surgery and once every three days for 9 days	Yes	-	E (~1.5 months)
Fish et al. (39)	2018	USA	P31	M	48	Toe	Left third toe osteomyelitis	Removal of free-floating proximal head of phalanx.	<i>Staphylococcus aureus</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Weekly application on wound for seven weeks	No*	No	A (~12 months)
			P32	F	27	Toe	Left second toe osteomyelitis	None	<i>Staphylococcus aureus</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Weekly application on wound for three weeks	No*	No	A (~41 months)
			P33	M	74	Toe	Right second toe osteomyelitis	Excision of base of middle phalanx	<i>Staphylococcus aureus</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Weekly application on wound for eight weeks	No*	No	A (-)
			P34	M	60	Toe	Left hallux osteomyelitis	None	<i>Staphylococcus aureus</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Weekly application on wound for eighteen weeks	No*	No	A (-)
			P35	F	71	Toe	Right second toe osteomyelitis	Removal of distal phalanx	<i>Staphylococcus epidermidis</i> + <i>Staphylococcus lugdunensis</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Three injections into distal toe tissue within a month	No*	No	A (~5 months)

Efremov et al. (40)	2018	Russia	P36	-	62	Tibia	Tibia osteomyelitis	Debridement + spacer implantation + PT , spacer explantation + internal fixation + PT	<i>Staphylococcus aureus</i> (MSSA)	-; phage cocktail; not tested for specificity	Topical (IOIA)	Once during surgery in the spacer, once during the second surgery in the cement	Yes	No	A (3.5 months)
Vogt et al. (41)	2017	Germany	P37	M	33	Knee	Knee PJI	Prosthesis explantation, spacer implantation, flap coverage, PT via surgically placed drains, amputation + PT	<i>Pseudomonas aeruginosa</i>	Commercial (GEI); phage cocktail; tested for specificity	Topical (IOIA)	Three times daily injections of phages via drainage tubes and one application during surgery	No*	No	E (-)
Samokhin et al. (42)	2016	Russia	P38-49	F (n=8) M (n=4)	58.4 ± 16.9 (mean and SD of n=12)	Hip (n=12)	Hip PJI (n=12)	One-stage cemented revision hip arthroplasty + PT (n=12)	<i>Staphylococcus epidermidis</i> (MSSE) (n=6) <i>Staphylococcus epidermidis</i> (MRSE) (n=3) <i>Staphylococcus aureus</i> (MSSA) (n=3)	Commercial (Microgen); -; tested for specificity (n=12)	Topical (IOIA) (n=12)	Injections (unspecified frequency) into drainage tubes for up to 10 days after surgery. (n=12)	Yes (n=12)	No (n=12)	A (n=10), C1 (n=1), C2 (n=1) (~6 months)
Fish et al. (43)	2016	USA	P50	M	92	Toe	Right second toe osteomyelitis	Removal of all visible bone	<i>Staphylococcus aureus</i>	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)	Weekly application on wound for four weeks	No*	No	A (-)
							P51	M	44	Toe	Right hallux osteomyelitis	None	<i>Staphylococcus aureus</i> (MRSA)	Commercial (GEI); single phage per bacteria; no specificity testing	Topical (sup.)

*In these cases, AB were not mentioned in the treatment protocol so the authors were contacted in order to confirm that none were given.

b If PJI was associated with a diagnosis of osteomyelitis, PJI was retained as the diagnosis (P13).

c On two occasions (P14, P28) not all phages used were tested for specificity prior to treatment.

Abbreviations

Ref.=reference

- = not reported

SD=standard deviation

M=Male; F=Female

PT=phage therapy; AB=antibiotics; SAT=suppressive antimicrobial therapy; PJI=periprosthetic joint infection; IV=intravenous; PO=*per os*

IOIA=intra-operative and/or intra-articular; sup.=superficial (on wound or into surrounding tissue)

DAIR=Debridement, Antibiotics and Implant Retention; DIEAP=Deep Inferior Epigastric Artery Perforator

GEI=George Eliava Institute or Eliava Biopreparations; QAMH=Queen Astrid Military Hospital; APT=Adaptive Phage Therapeutics

NB: The two records by Fish et al. (39) and (43) describe 3 identical cases (M, 74; M, 48; M, 60). They are presented once only here based on data from (39).

P1 was also published in a case series (44) not identified or retained in our search. Data concerning this patient was extracted from (26).

Information regarding whether a *Staphylococcus aureus* is MSSA (methicillin-sensitive *S. aureus*) or MRSA (methicillin-resistant *S. aureus*) is provided when available, as well as whether a *Staphylococcus*

