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Original article

Two-stage arthroplasty for septic arthritis of the hip and knee: A systematic review on infection control and clinical functional outcomes

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ABSTRACT

Introduction: Septic arthritis of the native hip and knee joint poses particular challenges to orthopedic surgeons. Patients often suffer from several comorbidities, and it could be challenging to find a balance between infection control and adequate function. Two-stage arthroplasty has been addressed as a reliable solution, however the literature on the topic is composed of case series with small sample size. This systematic review aimed to analyze data on infection control and clinical functional outcomes of patients who underwent two-stage arthroplasty for septic arthritis of the hip and knee.
Methods: An electronic search of studies published from January 1st, 2000, to June 1st, 2021, was conducted using eight different databases. Following the Cochrane Handbook of Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Revies and Meta-analysis two authors reviewed the available literature and reference lists to identify papers eligible for inclusion.
Results: A total of 21 studies were included, involving 435 procedures. The mean age was 57.3 ± 6.2 (45.8–71.8) years. The mean follow-up was 53.7 ± 18.6 (12–86.7) months. The mean infection eradication was 93.3 ± 6.4%. Mean Harris Hip Score improved from 32.1 ± 10.6 (11.5–42.9) to 87.5 ± 5.7 (80.6–97.8). Mean Knee Society Score improved from 42.9 ± 7.6 (35.9–58.0) to 86.1 ± 5.4 (80.1–96.0).
Conclusions: Two-stage arthroplasty for hip and knee septic arthritis provided high infection control rate and excellent function. Further high-quality studies should be oriented on providing a validated algorithm for diagnosis and treatment of this condition.
Level of evidence: Level IV, systematic review of Level III and IV studies.

1. Introduction

Patients affected by septic arthritis (SA) of the native hip or knee frequently experience significant pain and disability and are predisposed to life-threatening sequelae.[1,2] The management of this condition is challenging, and a multidisciplinary approach is recommended. SA often involves immunocompromised patients with severe comorbidities and should be considered a medical emergency, requiring prompt diagnosis and treatment.[1,3] Early-stage SA can be efficiently treated through antibiotics and arthroscopic irrigation and debridement.[4–6] Though chronic infections are associated with wider joint degeneration and the infectious process could cause cavitary bone defects, which management can be complex for the orthopedic surgeon.[7,8]

Several surgical strategies have been described in the literature to manage SA.[9] Historically, the Girdlestone procedure has been considered as a reliable solution to relieve pain and control infection in case of extensively damaged joint. However, the consequent leg-length discrepancy and the limited range of motion (ROM) significantly alter the function of the involved joint.[10,11]

Although total joint arthroplasty (TJA) has been addressed as a reliable solution in order to improve function, patients with previous SA are at higher risk for developing periprosthetic joint

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infections (PJI).[12–15]

However, to the best of our knowledge, there is no strong evidence in the literature to guide the surgical management of SA. Most of the literature on the topic is composed of relatively small retrospective series.

This study aimed to summarize current evidence on the clinical outcomes of patients who underwent a two-stage TJA in the setting of SA of the hip and knee. The primary endpoint of this systematic review was to analyze the rates of infection control provided by this surgical approach. The secondary endpoint was to report clinical and functional outcomes, expressed as clinical scores of validated objective and patient-reported outcome measures (PROMs). A summary of different diagnostic and surgical protocols is also provided.

2. Methods

2.1. Literature search and inclusion criteria

A systematic review of the literature has been performed, following the Cochrane Handbook of Systematic Reviews of Interventions[16] and the Preferred Reporting Items for a Systematic Reviews and Meta-Analyses (PRISMA)[17] for study selection (Fig. 1).

An electronic search from January 1st, 2000, until June 1st, 2021, was performed in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE/PubMed, Embase, Scopus, the Science Citation Index Expanded from Web of Science, ScienceDirect, CINAHL, and LILACS. The research was conducted using the following keywords: “septic arthritis”, “two-stage”, “total joint replacement”, “evolutive septic arthritis”, “hip arthritis”, “knee arthritis”, “two-stage replacement”, “arthroplasty”.

Original studies reporting clinical and functional outcomes of patients who underwent two-stage arthroplasties of the hip or knee with at least five patients were considered eligible for this analysis. Case reports, technical notes, abstracts, editorial commentaries, ex-vivo, pre-clinical studies (on animal or cadavers), and original studies reporting insufficient clinical data were excluded.

Two reviewers independently screened each title and abstract. Relevant titles and abstracts were collected, and the full-text assessment of papers was completed. The two reviewers independently followed the same checklist to screen all studies and evaluate the eligibility criteria. References of each study were retrieved and manually screened to detect any potential papers missed. Discussion between the two reviewers and a third senior author was used to resolve disagreements. A total of 1102 studies were initially identified for screening. After duplicates removal, 732 papers were excluded after the titles screening process. One-hundred-thirty-six studies were available for titles and abstracts assessment. Of these, 83 articles were excluded being focused on pathologies not related to SA, and 53 studies were available for full-text analysis. After the application of exclusion criteria, 21 studies were included in the systematic review (see Fig. 1). Seventeen were level of evidence IV papers, whereas four had a level of evidence III.

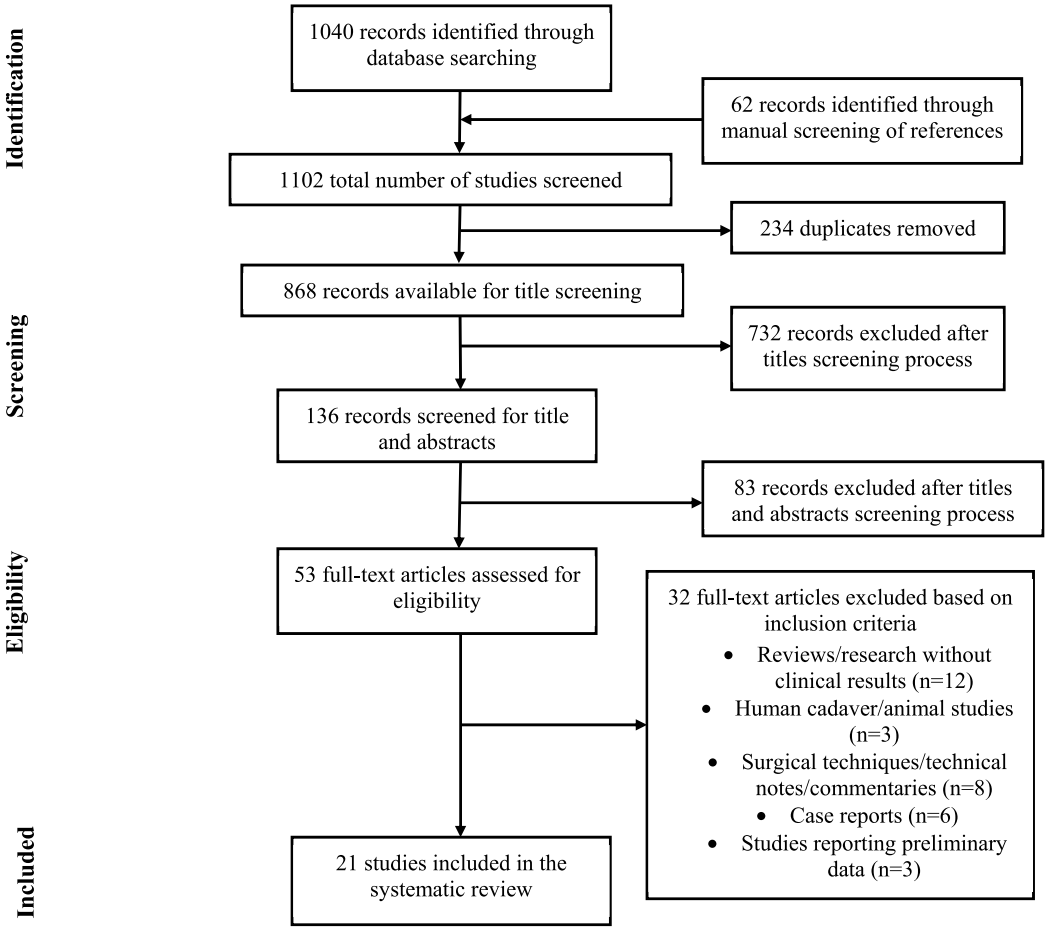

Fig. 1. PRISMA flowchart for studies selection.

2.2. Quality of the studies and risk of bias

The level of evidence of the included studies was evaluated through the adjusted Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[18]

The quality of studies was defined using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[19] system. No randomized controlled trials (RCT) were included. The risk of bias was classified using the Methodological Index for Non-Randomized Studies (MINORS).[20] Each item of the MINORS was scored 0 when absent, 1 when present but inadequate, and 2 when present and adequate. Ideal score for comparative studies was 24, and 16 for non-controlled studies. Comparative studies were classified as at high risk of bias if the overall score was ≤15, at moderate risk if it was >15 and ≤ 20, and at low risk of bias when >20. Non-controlled studies were considered at high risk of bias when the overall score was ≤8, at moderate risk when >8 and ≤ 12, and at low risk of bias when >12. The overall quality of the included studies was low (from moderate to very low), according to the GRADE system (Table 1). Detailed MINORS items and scores of each study are provided within Table 2. According to the MINORS criteria there were high risks of bias in six of the included studies, moderate risk in 13 studies, and low risk of bias in two. SI provides details on MINORS scores of each paper. Seventeen studies out of 21 were retrospective case series, three were retrospective series with a control group, and one was a prospective case series.

Table 1
Characteristics of the included studies grouped according to the joint involved. F female, L left, M male, m months, R right, SD standard deviation, y years, * data referring to the overall cohort of patients.

Main Author	Year	Country	Number of patients	Number of procedures	Side	Sex	Mean Age ± SD (range), y	Study design	Level of evidence	GRADE	Mean follow-up (range), m
Hip											
Chen[26]	2008	China	28	28	/	6 F 22 M	53 (27–35)	Retrospective case series	IV	Low	77 (30–151)
Diwanji[21]	2008	South Korea	9	9	/	4 F 5 M	53.3 (23–81)	Retrospective case series	IV	Low	42
Huang[30]	2009	Taiwan	14	15	/	5 F 9 M	54.3 (29–78)	Retrospective case series	IV	Very low	42.5 (25–72)
Kelm[31]	2009	Germany	8	8	/	4 F 4 M	66.5 (52–77)	Retrospective case series	IV	Very low	12 (5.2–24.8)
Bauer[29]	2010	France	13	13	/	/	60 (29–92)	Retrospective case series	IV	Low	60 (24–157) *
Fleck[22]	2011	USA	14	14	/	7 F 7 M	60.8 (45–87)	Retrospective case series	IV	Low	46.3 (13–80)
Romanò[23]	2011	Italy	19	20	/	10 F 9 M	55.7 (30–77)	Prospective case series	III	Moderate	56.6 (24–104)
Shen[24]	2013	China	5	5	/	3 F 2 M	48.4 (36–62)	Retrospective case series	IV	Very low	39.6 (30–59)
Anagnostakos[44]	2016	Germany	22	23	15 L 8 R	11 F 11 M	59.7 (32–78)	Retrospective case series	IV	Low	44.8 (12–120)
Papanna[43]	2018	UK	11	11	/	7 F 11 M	58 ± 11	Retrospective case-control	III	Moderate	70 (13–120)
Li[27]	2019	China	13	14	5 L 9 R	5 F 8 M	59.3 ± 4.3 (19–79)	Retrospective case-control	III	Low	21.1 (12–36)
Xu[46]	2019	China	55	55	/	14 F 41 M	45.8 ± 16	Retrospective case series	IV	Low	62
Kunze[25]	2020	USA	12	12	/	5 F 7 M	60.2 ± 15.2	Retrospective case series	IV	Low	39.6 ± 20.4 (24–121.2) *
Russo[48]	2021	Italy	25	25	19 L 6 R	12 F 13 M	56.4 ± 15.0	Retrospective case series	IV	Low	86.7 ± 16.0
Knee											
Nazarian[33]	2003	USA	14	14	/	5 F 4 M	62 (45–68)	Retrospective case series	IV	Low	54
Kirpalani[37]	2005	South Korea	5	5	2 L 3 R	5 F 0 M	71.8 (67–75)	Retrospective case series	IV	Very Low	38 (29–46)
Bauer[29]	2010	France	17	17	/	/	57 (31–82)	Retrospective case series	IV	Low	60 (24–157) *
Shaikh[35]	2014	South Korea	13	13	/	8 F 5 M	65.5 (39–81)	Retrospective case series	IV	Low	48 (24–84)
Yi[39]	2015	China	17	17	/	11 F 6 M	63.7 (43–74)	Retrospective case series	IV	Very Low	45.6 (24–96)
Xu[46]	2019	China	19	19	/	13 F 6 M	59.8 ± 13.6	Retrospective case series	IV	Low	40.3
Kunze[25]	2020	USA	30	30	/	11 F 19 M	57.4 ± 15.2	Retrospective case series	IV	Low	39.6 ± 20.4 (24–121.2) *
Ni[38]	2020	China	23	24	12 L 12 R	17 F 6 M	61.6 (45–75)	Retrospective case-control	III	Moderate	27.3 (12–54)
Pietsch[34]	2020	Austria	16	16	/	10 F 6 M	71.5 ± 12.4 (31–82)	Retrospective case series	IV	Low	73.2 (24–118.8)
Tahmesebi[45]	2020	Iran	6	6	/	4 F 2 M	50.5 (25–64)	Retrospective case series	IV	Very low	26 (12–40)
Russo[48]	2021	Italy	22	22	16 L 6 R	10 F 12 M	55.3 ± 13.9	Retrospective case series	IV	Low	85.6 ± 15.1

Table 2
MINORS criteria of the studies included in the systematic review.

First Author	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoint appropriated to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total points
Chen	2	1	0	2	1	2	0	0	-	-	-	-	8
Diwanji	2	2	0	2	1	1	2	0	-	-	-	-	10
Huang	2	2	0	2	1	1	2	0	-	-	-	-	10
Kelm	1	2	0	1	1	0	2	0	-	-	-	-	7
Bauer	2	2	0	2	1	2	2	0	-	-	-	-	11
Fleck	2	1	1	2	2	1	1	0	-	-	-	-	10
Romanò	2	2	2	2	2	1	2	0	-	-	-	-	13
Shen	0	2	0	1	1	1	2	0	-	-	-	-	7
Anagnostakos	2	2	1	1	1	1	2	0	-	-	-	-	10
Papanna	2	2	1	2	1	2	2	0	2	2	1	1	18
Li	2	0	0	2	2	0	2	0	2	2	1	1	14
Xu	2	1	1	2	2	2	2	0	-	-	-	-	12
Kunze	1	1	1	2	2	1	2	0	-	-	-	-	10
Nazarian	2	0	0	2	1	2	2	0	-	-	-	-	9
Kirpalani	1	0	0	1	1	1	2	0	-	-	-	-	6
Shaikh	1	0	1	1	1	2	2	0	-	-	-	-	8
Yi	2	0	0	2	1	2	1	0	-	-	-	-	8
Ni	2	0	0	1	2	1	2	0	2	2	2	2	16
Pietsch	2	2	1	2	2	2	2	0	-	-	-	-	13
Tahmesebi	1	1	1	2	1	1	2	0	-	-	-	-	9
Russo	2	2	2	1	2	2	0	0	-	-	-	-	11

2.3. Endpoints and statistical analysis

Primary endpoints of this analysis were the rates of infection control after stage one and after stage two respectively. Clinical and functional outcomes reported as patient-reported outcome measures (PROMs) or as objective clinical data and the rate of complications were the secondary endpoints.

Statistical analysis was focused exclusively on patients who underwent two-stage replacement of the hip or knee for SA. Continuous variables were reported as weighted means, and categorical variables as number of cases or percentage. Statistical analysis was conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, N.Y., USA).

General information of each study such as demographics, follow-up, diagnostic methods, etiology, pathogens involved, type of spacer, interval between stages, duration of antibiotic therapy were also extracted and tabulated. In case of studies with mixed cohorts, patients were pooled according to the joint affected. Infection eradication was defined as the absence of infection recurrencies. When both synovial and intraoperative microbiology were available, the latest one was considered for the analysis and recorded. Data were summarized in Tables 1 and 3.

3. Results

A total of 435 procedures on 430 patients were included in this review. The overall mean age was 57.3 ± 6.2 (range, 45.8–71.8) years. The overall mean follow-up was 53.7 ± 18.6 (range, 12–86.7) months. In 252 cases the joint involved in the septic process was the hip. The mean age of patients operated to the hip was 54.8 ± 5.7 (range, 45.8–66.5), with a mean follow-up of 56.2 ± 18.5 (range, 12.0–86.7) months. In the remaining 183 cases patients were operated to the knee. Their mean age was 60.8 ± 5.1 (range, 50.5–71.8). Mean follow-up of this cohort was 50.2 ± 18.2 (range, 26–73.2) months. Detailed demographics are displayed in Table 1.

3.1. Outcome measures

The score most frequently used for the assessment of hip function was the Harris Hip Score (HHS),[21] which preoperative and final values were reported in six studies.[18,22–26] Two studies reported only the HHS at final follow-up.[27,28] The Postel-Merle d'Aubigné (PMA)[29] score was used in three studies.[30–32]

The Knee Society Score (KSS)[33] and the Knee Society Score for Function (KSS–F) measured preoperatively and at last follow-up were reported in four and three studies, respectively.[18,26,34–36] The Hospital for Special Surgery (HSS) knee score[37] was used in three papers.[38–40] Less reported functional scores were the International Knee Society (IKS),[41] the Knee Injury and Osteoarthritis Outcomes (KOOS),[42] and the Western Ontario and McMaster University (WOMAC)[43] scores. See details in Table 3.

Thirteen studies reported details on comorbidities. Due to the scarcity of data a strict statistical analysis was not possible, however patients had a general high prevalence of diabetes mellitus (DM), chronic cardiovascular and pulmonary disease, organ failure, rheumatic disorders, human immunodeficiency virus (HIV), hepatitis-c virus (HCV), alcohol and drug abuse (Table 4).

3.2. Pathogens and diagnostic workup

Eighteen studies provided detailed information on causative pathogens. The most frequent pathogen involved was Staphylococcus aureus (139 cases, 32.0%); of these, 41 were resistant to antibiotics (methicillin or oxacillin). Coagulase-negative

Table 3

Diagnostic-therapeutic workups, clinical outcomes, and rates of infection eradication of the included studies. AZT aztreonam, *CLI* clindamycin, *CoNS* coagulase negative Staphylococcus, *CRP* C-reactive protein, *CT* computerized tomography, *DVT* deep venous thrombosis, *ERY* erythromycin, *ESR* erythrocyte sedimentation rate, *GEN* gentamicin, *HHS* Harris Hip Score, *HPF* high-power field, *HSS* Hospital for Special Surgery, *IKS* International Knee Society, *IV* intravenous, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *KSS* Knee Society Score, *KSS-F* Knee Society Score Function, *m* months, *LLD* leg length discrepancy, *MER* meropenem, *mHHS* modified Harris Hip Score, *MRI* magnetic resonance imaging, *MRSA* methicillin-resistant Staphylococcus aureus, *MSSA* methicillin-sensible Staphylococcus aureus, *PE* polyethylene, *PMA* Postel-Merle d'Aubigne, *PMN* polymorphonuclear, *ROM* range of motion, *SF* synovial fluid, *sp.* species, *STR* streptomycin, *TOB* tobramycin, *TBC* Tuberculosis, *THA* total hip arthroplasty, *TJA* total joint arthroplasty, *VAN* vancomycin, *VAS* visual analogue score, *w* weeks, *WBC* white blood cell count, *WOMAC* Western Ontario and McMaster University score, * data referring to the overall study population.

Main Author	Diagnosis			Intervention			Clinical functional outcomes	Complications	Infection eradication after first stage (%)	Infection eradication after second stage (%)
	Criteria	Etiology	Pathogens	Type of spacer	*Interstage interval ± SD (range), w*	*Duration of antibiotic therapy ± SD (range), w*				
Hip										
Chen[26]	. clinical evidence of SA . elevated ESR/CRP . positive culture . X-ray, CT, MRI	/	7 ORSA 7 OSSA 3 Polymicrobial 3 Salmonella 3 E. Coli 1 Pseudomonas sp. 1 Enterobacter 1 Enterococcus 1 Prevotella 1 Streptococcus	14 resections and cement beads (GEN)/14 Girdlestone	14.6 (4−28)	4 (2−17)	Postop HHS 80.6 (48−97)	2 reinfections after stage one 4 reinfections after THA 2 AL of the cup 3 periprosthetic fractures 1 stem broken	93	86
Diwanji[21]	. sinus tract communicating with hip . purulence at surgery . positive culture	/	4 MSSA 2 MRSA 2 Streptococcus 1 CoNS	Presterilized prosthetic stems + cement mantle (VAN or ERY)	24 (6.3−52.1)	/	Preop/postop HHS 38.4 (25−51)/97.8 (93−100)	1 reinfection after stage one (spacer exchange) 1 reinfection after THA	89	89
Huang[30]	. frank purulent fluid in operative exploration . CRP >20 mg/L . >5 WBC on histologic examination	/	4 MSSA 4 MRSA 3 Culture Negative 1 CoNS 1 Pseudomonas 1 Enterococcus 1 Morganella	Moulded cement (VAN + AZT) spacer with metallic endoskeleton	12.9 (6−31)	1 after stage one 3 after stage two	Preop/postop PMA score 9.3 (5−15)/16.7 (15−18)	1 reinfection (spacer exchange), 2 intraoperative periprosthetic fractures at stage two	93.3	100
Kelm[31]	. medical history . physical examination . elevated CPR . elevated ESR . radiological findings . isolation of the pathogen organism	4 post-surgery 2 contiguity 2 primaries	4 MSSA 2 Culture Negative 1 Streptococcus 1 Polymicrobial	Moulded femoral cement spacer (VAN)	90 (8.6−27.4)	6 after stage one	Preop/postop PMA score significantly increased ($p < 0.018$) Preop/postop Mayo hip score significantly increased ($p < 0.018$)	1 spacer dislocation 1 DVT 1 reinfection after THA	100	87.5
Bauer[29]	. clinical and biological inflammatory syndrome . functional deterioration of joint . radiological signs of cartilage and bone involvement	12 post-surgery 10 hematogenous *	9 St. Aureus 6 CoNS 3 Streptococcus 2 Gram-negative bacilli 2 Polymicrobial*	/	6 (4−16) *	13.3 (6.4−25.7) after stage one *	Postop PMA score 16.5 (14−18)	2 reinfections after THA	/	85
Fleck[22]	. purulence in the joint . ESR >30 mm/h/CRP >10 mg/L . positive intraop/aspiration cultures . >5 WBC frozen section spacer implantation . >3000 WBC in SF	9 primaries 2 post-infiltrative 3 post-surgery	3 MRSA 4 MSSA 3 Culture negatives 2 St. Epidermidis 1 Enterobacter 1 Polymicrobial	Prefabricated cement spacer (GEN or TOB + VAN + Ancef) w CrCo core and PE cup	10 (2−36)	6 after stage one	Preop/postop HHS 11.5 (0−52.8)/93.3 (66−100)	1 reinfection after stage one (spacer exchange)	90	100
Romanò[23]	at least three positives . ESR . CRP	11 post-surgery 8	7 MSSA 4 MRSA 3 CoNS	Prefabricated antibiotic loaded articulating spacer (GEN + VAN)	22.3 ± 5.1	5.2 ± 1.1 (4−6)	Preop/postop HHS 27.5 ± 15.3/ 92.3 ± 17.4	2 spacer dislocations 2 DVTs	100	95

(*continued on next page*)

Table 3 (*continued*)

Main Author	Diagnosis			Intervention			Clinical functional outcomes	Complications	Infection eradication after first stage (%)	Infection eradication after second stage (%)
	Criteria	Etiology	Pathogens	Type of spacer	*Interstage interval ± SD (range), w*	*Duration of antibiotic therapy ± SD (range), w*				
	. aspiration . frozen section . intraoperative cultures	hematogenous 1 post infiltrative	1 Enterococci 1 Pseudomonas sp. 4 Culture Negative				Preop/postop VAS 48 ± 20/8 ± 10	1 femoral nerve palsy 1 reinfection after THA		
Shen[24]	. frank purulent fluid or pus found by operative exploration . CRP >15 mg/L), . >10 PMN HPF	3 hematogenous 2 post-surgery	1 MSSA 1 MRSA 1 CoNS 1 TBC 1 Culture Negative	Handmade moulded cement with metallic pin (GEN + VAN)	18.6 (13−25)	At least 6 weeks after stage one	Preop/postop HHS 35.2 (28−43)/93.6 (89−99)	No complications	100	100
Anagnostakos[44]	. clinical (local redness, tenderness, effusion, painful range of motion) . radiological criteria . operative findings of purulence . CRP>20 mg/L . WBC> 10,000/ll, . microbiological and histopathological findings	/	/	Handmade cement spacer (GEN + VAN)	12.6 (3.7−37.3)	At least 6 weeks after stage one	/	3 spacer fractures (spacer exchange) 2 reinfections after stage one (spacer exchange) 2 spacer dislocations 7 draining sinuses 1 periprosthetic fracture 1 reinfection after THA	81	87
Papanna[43]	. clinical assessment . raised white cell count, c-reactive protein and erythrocyte sedimentation rate . blood culture . joint aspiration	12 primaries 5 hematogenous (drug abusers) 1 post-surgery *	11 MSSA 1 MRSA 1 Streptococcus 2 Polymicrobial*	Cement beads (VAN)	16 (12−20)	/	/	1 THA dislocation 2 heterotopic ossifications	100	100
Li[27]	. chronic sinus connected to the joint cavity . the presence of pus in the joint puncture or pus and destruction of femoral head during the surgery . CRP >20 mg/L . positive frozen sections during stage one . positive arthrocentesis or intraoperative cultures	9 primaries 5 post-surgery	3 MSSA 2 MRSA 2 Culture Negative 1 Burkholderia 1 Stenotrophomonas 1 E. coli 1 Enterobacter 1 Corynebacterium 1 Streptococcus	4 Girdlestone/11 prefabricated or handmade cement spacers	52.4 (12−276)	9.4 (6−24)	Post HHS Gridlestone group 81.6 ± 1.1/Spacer group 88.9 ± 1.7	1 spacer fracture 2 delayed wound healing	100	100
Xu[46]	. clinical signs of infection . radiographic finding . CRP >10 mg/dL . ESR >30 mm/h . purulence during operations . positive synovial cultures or at stage one	38 post-surgery 5 hematogenous 3 post-infiltrative 9 unknowns	2 St. Aureus 2 Resistant organism 15 CoNS 6 Gram-negative 8 Other organisms 5 polymicrobial 17 Culture Negative	Handmade articulating cement spacer (VAN + MER)	/	/	/	3 spacer fractures 2 spacer dislocations	93	89
Kunze[25]	. history of a remote or acute pyogenic arthritis of the affected joint	/	11 Culture Negative 6 MSSA 4 MRSA 10 CoNS 1 Serratia marcescens 1 Pseudomonas	Hand moulded or prefabricated articulating cement spacer (VAN + TOB)	/	6 after stage one	Preop/postop mHHS 42.9 ± 11.8/ 83.3 ± 11.1 Preop/postop ROM 73.8 ± 21.2/ 102.1 ± 11.8	1 reinfection after stage one (spacer exchange) 1 THA dislocation	91.7	100

			3 Streptococcus 1 Polymicrobial 5 Not available*							
Russo[48]	. clinical signs of infection . CRP >5 mg/dL) . ESR >30 mm/h) . radiographic findings of bone resorption and loss of articular space . intra-operative purulence . positive intra-operative or synovial fluid microbiology	4 post-surgery 2 post-infiltrative 19 primary	7 MSSA 3 MRSA 1 Streptococcus 2 Pseudomonas 2 Mycobacterium 1 E. Coli 1 Proteus 2 Polymicrobial 6 Culture Negative	Prefabricated antibiotic loaded stem spacer (GEN + VAN) + handmade acetabular spacer	14.5 ± 2.9	At least 6 after stage one	Preop/postop HHS 39.4 ± 9.9/84.5 ± 10.8 Preop/postop offset 51.1 ± 5.0/52.0 ± 4.6 Postop LLD 7.4 ± 7 mm	1 reinfection after stage one (spacer exchange) 2 reinfection after THA 5 heterotopic ossification 1 hematoma	96	92
Knee										
Nazarian[33]	. clinical presentation . radiographic findings . aspiration of the knee joint	6 post-surgery 8 primaries	3 St. Aureus 2 St. Epidermidis 2 Streptococcus 1 E. Coli 6 Culture Negative	Hand moulded spacer block (VAN + TOB)	12.4 (6 −32.8)	At least 6 stage one/24 after stage two	Preop/postop KSS 46/89 Postop ROM 3°−105° (0−125°)	1 hematoma requiring evacuation 1 DVT 1 wound healing complication (skin graft)	100	100
Kirpalani[37]	. joint aspiration . arthroscopy	4 post-infiltrative 1 primary	4 MSSA 1 MRSA	Cement beads	7 (6−8)	/	Postop HSS pain 83 (80−85) Postop HSS function 73 (65−82) Postop ROM 5°−104° (5°−120°)	1 symptomatic heterotopic ossification	100	100
Bauer[29]	. clinical and biological inflammatory syndrome . functional deterioration of joint . radiological signs of cartilage and bone involvement	15 post-surgery 10 hematogenous 6 post-infiltrative *	10 St Aureus 8 CoNS 6 Streptococcus 4 Gram-negative bacilli 3 Polymicrobial *	/	6 (4−16) *	13.3 (6.4 −25.7) after stage one *	Postop IKS Knee Score of 83 (65−100) Postop IKS Functional Score of 80/100 (40−100)	2 reinfections after TKA	/	88
Shaikh[35]	. aspiration of infective joint fluid (WBC count, PMN percentage) . isolation of organism(s) from joint fluid . presence of a draining sinus . MRI evidence of a septic knee combined with osteomyelitis	7 post-surgery 6 primaries	2 MRSA 1 MSSA 2 Candida Sp. 1 Pseudomonas Sp. 7 Culture Negative	Handmade articulating cement spacer (VAN + STR)	22.4 (8 −116)	(4−12) after stage two	Preop/Postop KSS 41(26−73)/85 (46 −93) Preop/postop KSS-F 43 (27−73)/83 (47 −92) Preop/postop WOMAC 51 (40−65)/18 (11 −31) Preop/postop ROM 103° (range, 60° −155°)/115° (range, 75°−150°) Preop/postop VAS 66 (50−75)/18 (0 −40)	1 reinfection after stage one (spacer exchange)	76.9	100
Yi[39]	. elevated CRP and ESR . radiologic findings . SF cultures . clinical signs . temperature >38 °C	8 post infiltrative 4 post-surgery 2 post-traumatic 3 primaries	4 CoNS 1 MRSA 1 MSSA 6 Culture Negative 1 Pseudomonas sp. 2 Not Available	Moulded articulating cement spacer (VAN + GEN)	16.8 (10 −27)	4 after stage two	Preop/postop HSS 37.7 (19−56)/83.9 (77−91) Preop/postop ROM 12.1-64-7° (5−100°)/ 1.6−107.5° (0−125°)	1 reinfection after stage one (arthrodesis)	94.1	100
Xu[46]	. clinical signs of infection, . radiographic finding . CRP >10 mg/dL . ESR >30 mm/h	8 post-surgery 2 hematogenous 5 post-	4 St. Aureus 2 Resistant organism 1 Gram-negative	Handmade articulating cement spacer (VAN + MER)	/	/	/	/	100	84

(continued on next page)

Table 3 (*continued*)

Main Author	Diagnosis			Intervention			Clinical functional outcomes	Complications	Infection eradication after first stage (%)	Infection eradication after second stage (%)
	Criteria	Etiology	Pathogens	Type of spacer	*Interstage interval ± SD (range), w*	*Duration of antibiotic therapy ± SD (range), w*				
	. purulence during operations . positive synovial cultures or at stage one	infiltrative 4 unknowns	4 Other organisms 1 Polymicrobial 7 Culture Negative							
Kunze[25]	. history of a remote or acute pyogenic arthritis of the affected joint	/	11 Culture Negative 6 MSSA 4 MRSA 10 CoNS 1 Serratia marcescens 1 Pseudomonas sp. 3 Streptococcus 1 Polymicrobial 5 Not available*	27 articulating/3 static handmade cement spacer (VAN + TOB)	/	6 after stage one	Preop/postop KSS 35.9 ± 16.9/ 80.1 ± 16.6 Preop/postop KSS-F 38.0 ± 15.1/ 71.5 ± 24.0 Preop/postop ROM 90.9 ± 14.9/ 100.5 ± 17.1	4 reinfections after stage one (spacer exchange) 2 reinfections after stage two 4 arthrofibrosis 1 patellar instability (lateral release and liner exchange)	86.7	93.3
Ni[38]	. symptoms and signs of clinical infection . CRP >10 mg/dL . ESR >30 mm/h . PMN >90% . imaging . purulence at surgery . > 5 neutrophils/HPF at froze sections . positive synovial fluid or tissue culture	13 post-infiltrative 4 post-surgery 7 primaries	3 St. Aureus 2 CoNS 3 Polymicrobial 3 Candida sp. 1 Micrococcus luteus 1 Propionibacterium acnes 1 Aspergillus flavus 10 Culture Negative	9 handmade tibial plateau spacer/15 cement beads (VAN + MER)	/	At least 6 weeks after stage one	Group A preop/ postop HSS Knee Score 36.9 ± 12.9/90.5 ± 5.5 Group B preop/ postop HSS Knee Score 30.5 ± 11.0/ 80.9 ± 13.5 Group A preop/ postop ROM 66.2 ± 27.9°/ 109.4 ± 18.1° Group B preop/ postop ROM 47.7 ± 26.2/ 96.0 ± 23.3	2 reinfections after stage one (spacer exchange)	83.3	100
Pietsch[34]	. clinical signs of infection . synovial WBC> 50,000 cells/mm and PMN ≥90% . synovial cultures . elevated CPR and ESR	/	4 MSSA 3 MRSA 2 CoNS 3 Streptococcus 1 Corynebacterium 3 Culture Negative	Prosthetic femoral component, tibial polyethylene liner and cement mantle (GEN + CLI + VAN)	6	2 IV 4 p.o. after stage one	Preop/postop KSS 58 ± 12/96 ± 3 Preop/postop KSS-F 17 ± 11/86 ± 6 Preop/postop VAS 65 ± 11/1 ± 2 Preop/postop ROM 95 ± 30°/119 ± 10°	No complications	100	100
Tahmesebi[45]	. joint tap cell counts . acute inability of patient for weightbearing . recent joint swelling and hotness	/	3 St. Aureus 1 CoNS 1 Enterococcus 1 Polymicrobial	Static cement block spacer (VAN)	8	6 after stage one	Postop KOOS 84.8 (75–95) Preop/postop ROM 0–104°/0–123°	No complications	100	100
Russo[48]	. clinical signs of infection . CRP >5 mg/dL) . ESR >30 mm/h) . radiographic findings of bone resorption and loss of articular space . intra-operative purulence . positive intra-operative or synovial fluid microbiology	13 post-surgery 4 post-infiltrative 5 primary	6 MSSA 3 MRSA 3 CoNS 2 Streptococcus 1 Pseudomonas 2 Mycobacterium 2 Polymicrobial 5 Culture Negative	Prefabricated antibiotic loaded articulating spacer (GEN + VAN)	14.9 ± 2.8	At least 6 after stage one	Preop/postop KSS 40.7 ± 8.4/86.0 ± 7.8 Preop/postop KSS-F 25.7 ± 14.2/ 85.4 ± 23.4	1 reinfection after stage one (spacer exchange) 1 aseptic loosening after stage two 2 reinfection after TKA 1 extensor mechanism disruption	95.5	90.9

Table 4
Patients' comorbidities reported in the included studies. CHD chronic heart disease, *CPD* chronic pulmonary disease, *DM* diabetes mellitus, *HCV* hepatitis-c virus, *HIV* human immunodeficiency virus, *NR* not reported, *RA* rheumatoid arthritis, *TBC* tuberculosis. * data relative to the overall population.

Main Author	Comorbidities (n)
Hip	
Chen[26]	DM (3), hepatic insufficiency (3), peptic ulcer (3), adrenal insufficiency (3), gouty arthritis (2), hypertension (2), drug addiction (2), neoplastic disease (3), pulmonary TBC (1)
Diwanji[21]	NR
Huang[30]	DM (4), alcoholism (4), SLE (4), hepatic insufficiency (3), neoplastic disease (2), renal insufficiency (2), adrenal insufficiency (1), drug abuse (1)
Kelm[31]	CHD (6), arterial hypertension (4), DM (2), obesity (2), alcohol abuse (2), neoplastic disease (2), CPD (2), CRD (2), renal TBC (1)
Bauer[29]	NR
Fleck[22]	NR
Romanò[23]	NR
Shen[24]	NR
Anagnostakos[44]	DM (8), arterial hypertension (8), CHD (4), CRD (4), neoplastic disease (3), hypothyroidism (2), drug abuse (2), HCV (2), HIV (1), renal TBC (1), epilepsy (1)
Papanna[43]	NR
Li[27]	DM (4), arterial hypertension (2), CPD (1), cirrhosis (1), syphilis (1), osteoporosis (1), gout (1), eczema (1)
Xu[46]	DM (9), RA (4), smokers (11), alcohol abuse (10), CHD (7), CPD (3) *
Kunze[25]	NR
Russo[48]	DM (7), drug abuse (6), HIV (5), HCV (4), TBC (1), CHD (8), CPD (4), epilepsy (2)
Knee	
Nazarian[33]	Obesity (5), RA (2), DM (2), renal insufficiency (1), hepatic insufficiency (1)
Kirpalani[37]	DM (1), contralateral OA (1)
Bauer[29]	NR
Shaikh[35]	DM (4), CPD (1), polytrauma (1), spine infection (1), Addison disease (1)
Yi[39]	NR
Xu[46]	DM (9), RA (4), smokers (11), alcohol abuse (10), CHD (7), CPD (3) *
Kunze[25]	NR
Ni[38]	NR
Pietsch[34]	DM (6), obesity (6), chronic polyarthritis (1), psoriasis (1)
Tahmesebi[45]	NR
Russo[48]	DM (5), drug abuse (4), HIV (3), HCV (4), CHD (6), CPD (5), epilepsy (1)

Staphylococci were involved in 58 (13.3%) cases. In a high percentage of patients (93 cases, 21.4%) cultures were negatives.

The diagnostic pathway was highlighted in all the studies. Although there was no homogeneity in criteria adopted, a complete diagnostic workup should include clinical, laboratory, imaging, and intraoperative findings. Most used clinical signs of infection were the presence of a sinus tract communicating with the joint, local redness, tenderness, effusion, and painful ROM. Imaging methods described were radiographs, magnetic resonance imaging (MRI), and computed tomography (CT) of the involved joint. Laboratory tests used were serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, synovial WBC count, and synovial microbiology. Intraoperative macroscopic purulence, histology and microbiology of surgical samples were frequently adopted to address diagnosis to SA.

Details on pathogens and diagnostic workups are shown in Table 3.

3.3. Surgical protocols

In all but 18 (4.1%) two stage procedures the positioning of a spacer at stage one in association with joint resection and debridement was involved.

Description of the type of spacer used was provided in 20 studies.[18,22–28,31,32,34–36,38–40,44–48] In 45 patients cement beads were used as a spacer.[27,38,39,45] Three authors described the use of prosthetic components covered with a bone cement mantle.[22,23,35] In five studies the use of a prefabricated cement spacer was described.[18,23,24,28,48] In the remaining cases, handmade spacers, or spacers moulded at time of surgery were used. Seventeen authors used antibiotic-loaded cements. The most frequently antibiotics used in cement were vancomycin and gentamicin. The mean time from stage one to stage two ranged from 6 to 90 weeks. Duration of antibiotic therapy ranged from 6 to 9.4 weeks after the first stage, and from 4 to 24 weeks after stage two.

3.4. Control of infection

The overall mean percentage of infection eradication after stage one and stage two were 92.9 ± 6.4% and 93.3 ± 5.8%, respectively. In patients who underwent hip surgery, infection was considered controlled in 93.5 ± 5.3 (range, 81.0–100.0) % of cases after stage one, and in 92.1 ± 5.5 (range, 85.0–100.0) % after stage two. In patients operated to the knee, the infection was considered resolved in 92.2 ± 7.7 (range, 76.9–100) % of cases after stage one, and in 95.0 ± 5.7 (range, 84.0–100.0) % of cases after stage two.

3.5. Functional outcomes

Mean scores of clinical functional questionnaires at final follow-up ranged from good to excellent.

Preoperative HHS values of in 85 patients were available and the weighted mean was 32.1 ± 10.6 (range, 11.5–42.9) points. HHS was collected from 127 patients at final follow-up with a mean value of 87.5 ± 5.7 (range, 80.6–97.8) points. Mean PMA at final follow-up was obtained from 28 patients and it was 16.6 ± 0.1 (range, 16.5–16.7).

Mean values of preoperative KSS and at final follow-up, collected from 95 patients, were 43.9 ± 7.6 (range, 35.9–58.0), and 86.1 ± 5.4 (range, 80.1–96.0), respectively. KSS-F was reported in 81 patients. Mean preoperative values and at final follow-up were 31.3 ± 9.4 (range, 17.0–43.0) and 80.0 ± 6.6 (range, 71.5–86.0), respectively. Preoperative HSS was gathered from 41 patients and averaged 34.9 ± 2.4 (range, 32.9–37.7). HSS for knee was collected form 46 patients and its mean value was 83.6 ± 2.0 (range, 78.0–84.5).

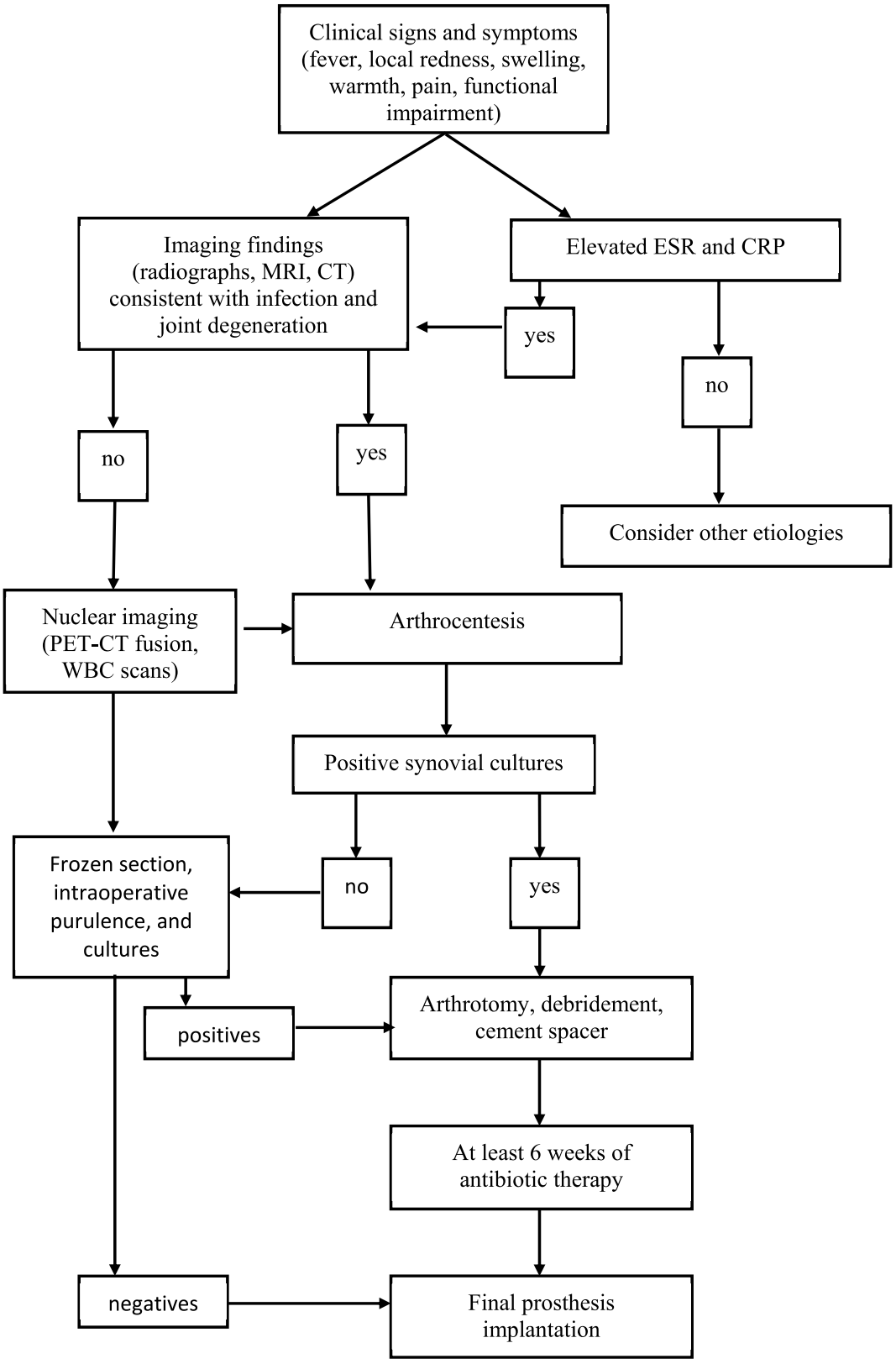

Fig. 2. Flowchart resuming the diagnostic workup and management of degenerative septic arthritis of the native hip or knee.

Values of IKS, KOOS, and WOMAC are listed in Table 3.

3.6. Complications

The overall number of complications reported was 88 (20.2%). Septic recurrencies during the interstage period were reported in 18 (4.1%, 9 hips and 9 knees) cases. Among these, 15 were successfully managed through spacer exchange, and in one case knee arthrodesis was performed. Septic recurrencies after TJA were described in 18 (4.1%, 12 hips and 6 knees) cases. Spacer-related complications occurred in 14 (3.6%) cases. Of these, seven were hip spacer dislocations, and seven were hip spacer fractures. In 10 (2.6%) cases complications of the surgical wound, such as draining sinus and delayed healing, occurred. Periprosthetic fractures of the hip were registered in six cases (1.5%). Less frequent complications were deep venous thrombosis (DVT, 4 cases), arthrofibrosis (four cases), symptomatic heterotopic ossifications (8 cases), THA dislocations (2 cases), aseptic loosening (3 cases), one case of patellar instability requiring lateral release and liner exchange, and one major hematoma of the knee that required surgical drain (Table 3).

4. Discussion

The most relevant finding of this review is that a two-stage arthroplasty approach to SA of the hip and knee provides a high rate of infection control (93.3 ± 5.8%) at mid-term follow-up (53.7 ± 18.6 months). Furthermore, this study demonstrated that such an approach is able to provide good to excellent results in term of joint function.

Prompt diagnosis of SA is mandatory for optimal recovery, and it should be considered one of the most important prognostic factors. Nevertheless, a delay in diagnosis and treatment is still a matter of concern in everyday clinical setting. SA remains a challenging diagnosis. Despite scientific literature provides several diagnostic algorithms for PJI, adult SA lacks such high quality algorithmically validated diagnostic workup.[49,50]

A complete medical history is of a paramount importance in the evaluation of a patient with suspected SA. In the cohort of patients of whom comorbidities were reported (238), 22.5% were affected by DM, 12.6% suffered from autoimmune diseases, 11.5% were drug or alcohol abusers, and 8.4% had organ insufficiency. Then, SA should always be considered as a differential diagnosis in patients which suffer from these comorbidities.

According to the data of the present review, SA suspicion is mainly based on clinical findings and serum laboratory examination. Final diagnosis is eminently guided by synovial fluid analysis, intraoperative findings and synovial fluid or tissue specimens' culture.

Radiological and functional imaging have limited role in PJI diagnosis. On the contrary, radiographic features such as acetabular involvement in chronic hip SA, MRI bone involvement especially on T2-weighted scans and functional imaging (WBC scans or PET-CT fusion imaging) should provide additional information on SA extension (osteomyelitis, periarticular abscess) and could guide surgical debridement (Fig. 2).

Over the years several surgical approaches have been investigated in order to treat active SA of the hip and knee, like arthroscopic debridement, Girdlestone procedure, and one-stage TJA.[9] The arthroscopic approach is a viable minimally invasive solution in case of early stages SA but has a limited therapeutic potential in case of SA with a wide articular degeneration.[4,51,52] Though, arthroscopy can be considered when suspecting SA of the knee and hip, due to its strong diagnostic power. Girdlestone procedures can be a viable solution in order to control infection in low-demanding older patients with several comorbidities, but the impairment of function inherent to this approach is not acceptable in more active patients.[10,11] On the other hand, one-stage arthroplasty can provide better functional results, but the risk of subsequent PJI is still a concern, then it should be considered an advisable approach only in patients with a previous SA which is quiescent at time of surgery.[13,45] However, the timing to consider SA quiescent in order to safely perform a one-stage arthroplasty is not clear and a proper workflow that include synovial fluid analysis is mandatory. As recently reported by Tan et al.[3] antibiotic-resistant organisms, male gender, DM, and a postsurgical cause of SA seem to be risk factors for developing PJI after joint replacement for SA.

During the interstage period, the use of a cement spacer is useful to provide acceptable function, to maintain limb length, and it is thought to have a local microbicide potential when loaded with antibiotics.[53] However, spacer related complications are still a concern when considering indication to two-stage arthroplasty.[54,55] In the cohorts of patients herein analyzed spacer-specific complications, as spacer dislocations and spacer fractures, accounted for 17.5% of the total number of complications. During the interim spacer period the most frequent complications was the recurrence of infection, which however it had been successfully managed in all cases through spacer exchange.

It is important to note that several limitations characterize this study. Firstly, the majority of studies included were level of evidence IV retrospective studies, addressing this review to the bias specific of this kind of papers. No RCT or prospective controlled studies comparing two-stage arthroplasty to other treatments are available in the literature, and their production should be encouraged. Moreover, different types of etiology were all considered together, since a systematic analysis for subgroups was not possible due to the scarcity of data on clinical results pooled for subgroups. It must also be considered that being all but one of the studies included retrospective, the real rates of complications is likely to be higher than those reported since minor complications could have been missed.

5. Conclusions

Two-stage arthroplasty guarantees high infection control rates in the setting of SA of the hip and the knee, and it is associated with good to excellent results in terms of joint function. Spacer-specific complications have a low prevalence and can successfully be managed through spacer exchange or conversion to TJA. Further high-quality studies should be oriented on providing a validated algorithm for diagnosis and proper treatment of SA.

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CRediT authorship contribution statement

Antonio Russo: Conceptualization, reviewer, Formal analysis, Writing – original draft. **Luca Cavagnaro:** reviewer, Methodology, Writing – original draft. **Mattia Alessio-Mazzola:** Writing – review & editingediting of the Writing – original draft. **Lamberto Felli:**

senior reviewer, Supervision, Project administration. **Giorgio Burastero:** senior reviewer, Supervision, Project administration. **Matteo Formica:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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