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ORIGINAL RESEARCH

Chronic infections in hip arthroplasties: comparing risk of reinfection following one-stage and two-stage revision: a systematic review and meta-analysis

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Background: Two-stage revision is regarded by many as the best treatment of chronic infection in hip arthroplasties. Some international reports, however, have advocated one-stage revision. No systematic review or meta-analysis has ever compared the risk of reinfection following one-stage and two-stage revisions for chronic infection in hip arthroplasties.

Methods: The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Relevant studies were identified using PubMed and Embase. We assessed studies that included patients with a chronic infection of a hip arthroplasty treated with either one-stage or two-stage revision and with available data on occurrence of reinfections. We performed a meta-analysis estimating absolute risk of reinfection using a random-effects model.

Results: We identified 36 studies eligible for inclusion. None were randomized controlled trials or comparative studies. The patients in these studies had received either one-stage revision (n = 375) or two-stage revision (n = 929). Reinfection occurred with an estimated absolute risk of 13.1% (95% confidence interval: 10.0%–17.1%) in the one-stage cohort and 10.4% (95% confidence interval: 8.5%–12.7%) in the two-stage cohort. The methodological quality of most included studies was considered low, with insufficient data to evaluate confounding factors.

Conclusions: Our results may indicate three additional reinfections per 100 reimplanted patients when performing a one-stage versus two-stage revision. However, the risk estimates were statistically imprecise and the quality of underlying data low, demonstrating the lack of clear evidence that two-stage revision is superior to one-stage revision among patients with chronically infected hip arthroplasties. This systematic review underscores the need for improvement in reporting and collection of high-quality data and for large comparative prospective studies on this issue.

Keywords: infection, arthroplasty, hip replacement, one-stage, two-stage, reoperation

Introduction

Much has been written in past decades on the treatment of infected hip arthroplasties (HA), as infection constitutes a major cause of revision.[1] The incidence of deep infection following HA has stabilized at less than 1%.[2–5] This severe complication to an otherwise very successful procedure is a large personal and economic burden to the patient and very costly from a societal perspective.[4,6,7] Current treatment options involve a panel of surgical and nonsurgical approaches.[8] Antibiotic suppression therapy is used if the patient is very ill or declines further surgical treatment.[8,9] Debridement and

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antibiotic treatment combined with implant retention is used in early and acute hematogenous infections, but is inferior in chronic infections.[10–12] Direct exchange (one-stage revision) or delayed reimplantations (primarily as two-stage revision) are used in chronic infections. Two-stage revision is currently regarded as the surgical gold standard worldwide.[8,9,13–16] The one-stage approach, pioneered by Buchholz three decades ago, is advocated mainly by European centers.[15,17] One-stage revision has the presumed advantages of a lower personal burden for the patient, a societal economic gain, and an overall better outcome due to fewer surgical procedures and lack of an interim period. The last large review on one-stage revision in the treatment of infected HA was published a decade ago.[18] The authors concluded on the basis of 1299 episodes of infected HA treated by one-stage revision that the indication for one-stage revision was limited due to a high reinfection risk (17% reinfected). The risk estimate was obtained by pooling cases from twelve studies. Cases represented a mixture of acute and chronic infections, and no evaluation of the quality of the research data was performed. Furthermore, no direct comparison was made with other treatment strategies. We found it appropriate to investigate systematically the current evidence for best practice in the treatment of chronic infections in HA, with a focus on retention of a functional hip implant. We performed, to our knowledge, the first systematic review and meta-analysis comparing the risk of reinfection following one-stage and two-stage revision for chronic infection in HA.

Materials and methods

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[19,20] Our aim was to examine whether one-stage revision is a relevant treatment strategy for chronic infection in HA with respect to the primary-outcome reinfection, as compared to the currently accepted gold standard of two-stage revision. All types of study designs were accepted for inclusion in this review.

Search strategy

Studies were identified by electronic-database searching of PubMed (1966–May 2010), Embase (1980–May 2010), the Cochrane Library, and the World Health Organization platform for international clinical trials registries (http://www.who.int/ictrp). We used a search strategy developed by the first author and a university research librarian, as specified in Table 1.[21]

Table 1 Search strategy

Search performed in the following numerical order (Pubmed/Embase)
#1 Hip arthroplasties
#2 Hip replacement
#3 Hip replacements
#4 Replaced hip
#5 Hip implant
#6 Hip implants
#7 Hip joint replacement
#8 Hip joint replacements
#9 Total hip prosthesis
#10 Hip prostheses
#11 Infection OR infections
#12 One stage OR 1stage
#13 Two stage OR 2 stage
#14 Delayed reimplantation OR stage reimplantation OR staged reimplantation
#15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#16 #12 OR #13 OR #14
#15 #11 AND #15 AND #16

Notes: The search strategy was applied as key concepts. No limits applied. The Cochrane Library was searched using: infection AND hip/infection AND arthroplasty/infection AND hip replacement. The World Health Organization platform for international clinical trials registries (http://www.who.int/ictrp) was searched for ongoing, terminated, or completed trials using: infection AND hip/infection AND arthroplasty/infection AND hip replacement. Keywords used to assess relevancy in the electronic database search: hip, infected, infection, bacteria (or specific species), septic, one-stage, two-stage, direct exchange, exchange, stage, staged, revision, arthroplasty, replacement, prosthesis, treatment, spacer, beads, outcome.

Reference lists of all acquired original and review articles were assessed for relevance and cross-referenced with articles already obtained ("snowballing"). Studies were subjectively assessed by title in the electronic-database search (see criteria used in Table 1), and if deemed relevant, the abstract was retrieved. In cases of possible relevance based on the abstract, the full-length text was obtained. In cases where no abstract was available, the full-length text was obtained.

Eligibility criteria

From the full-length texts obtained, we included all studies that examined patients with an HA and a diagnosed infection of the implant, for whom a defined duration of symptoms or time period from the index implantation to the infection diagnosis was given, who were treated with either one-stage or two-stage revision, and for whom data on occurrence and number of reinfections were available. Selected relevant patient subgroups from broader studies were also able to be included. No restrictions were made according to age, gender, presence of comorbidity, infecting microorganism, primary hip disease, and nature of the index implant or length of patient follow-up. We did not include patients who had

received treatment for a new infection following a prior septic revision, regardless of time interval, or patients who did not complete a reimplantation as part of a planned two-stage revision but were discharged following a Girdlestone/permanent-spacer procedure. We chose to compare only patients with completed one-stage and completed two-stage revision, as we considered this the clinically relevant treatment exposure of interest. Only patients reported in full-length articles were included for analysis. Studies with overlapping patient data were individually assessed and the most appropriate study chosen for inclusion (based on available information and longest follow-up). Eligibility assessment was done by the first author.

Data processing

The following variables were registered: (1) main exposure – patients undergoing one-stage/two-stage revision with completed reimplantation; (2) primary outcome – reinfection; (3) study demographics – first author, publication year, the institution where patients were operated on, the calendar period of inclusion, presence of a study hypothesis, a predefined primary end point, clearly defined in- and exclusion criteria, study design, retrospective or prospective data collection; (4) study population demographics – definition of infection, defined time period between latest surgery to the hip and subsequent infection, duration of infection symptoms prior to revision, the total number of patients eligible for reimplantation,

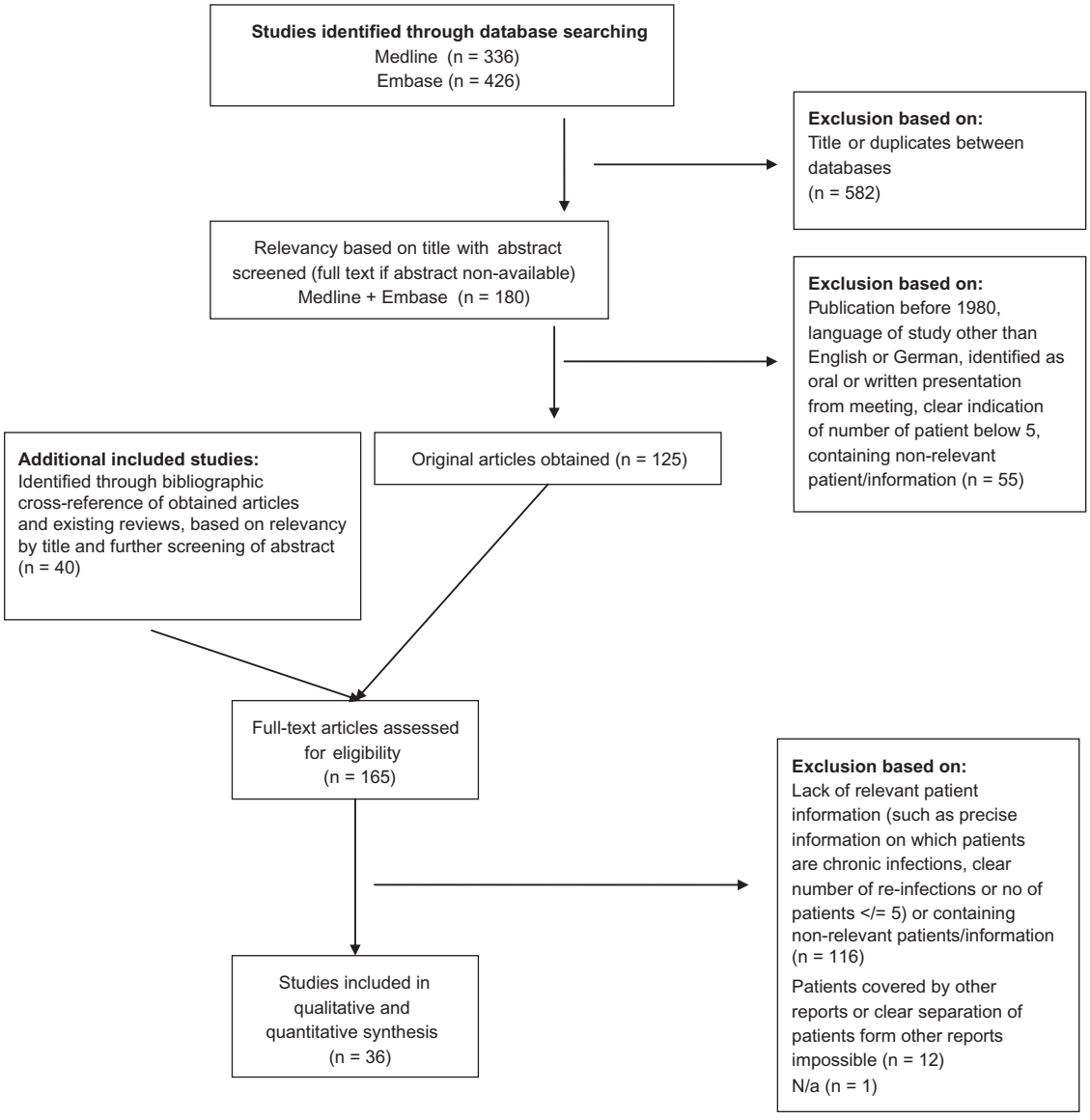

Figure 1 PRISMA flow diagram.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

study size (total number of patients receiving reimplantation), gender, age, patient comorbidity, data on the infected index HA (primary/revision and cemented/cementless), revision for other cause than infection after reimplantation; and (5) perioperative setting – type of implant used at reimplantation (cemented/cementless), follow-up period, microbiological cultures for individual patients, patient assessment score after revision surgery, time interval between stages, the use of spacer/beads or other topical antibiotics, antibiotic treatment regimen. Data were extracted independently by the first and second authors. Disagreement was resolved by consensus.

Summary measures

We performed meta-analysis estimating the absolute risk (hereafter referred to simply as "risk") with 95% confidence intervals of the primary outcome with a random-effects model. The analysis was performed using extracted patient data from the individual studies. Subgroup analysis on the risk of reinfection was done for main exposure and further stratified by type of implant used at reimplantation. We performed meta-regression for all studies and stratified by main exposure regarding study size and publication year on risk of reinfection. We performed sensitivity analysis by means of "one-study removed" to detect outliers and evaluate single-study impact on the derived estimates. By a priori acknowledgment of significant inconsistency among studies and by taking this into account using a random-effects model, we did not further quantify existing heterogeneity.[22] All data management was done using Comprehensive Meta-Analysis (v2.0; BioStat, Englewood, NJ). In the case of zero-outcome events, this program adds 0.5 to the value of both outcome events and sample size and uses these modified values for all future calculations (eg, no events in 20 patients: 0.5/20.5 = risk of 0.024). Forest plots were produced to qualitatively evaluate study heterogeneity and graphically support risk estimates. Funnel plots were used to graphically assess the possibility of publication bias. Such bias was believed a priori to exist for small studies with poor results.[23] Assessment of methodological or clinical limitations for the included studies was done with a focus on key study features, these being: (1) patient sample – well-defined inclusion criteria, mode of data collection, defined patient demographics; (2) follow-up – sufficiently defined as more than 2 years; (3) outcome – adequate description regarding infection diagnosis; and (4) treatment – perioperative treatment regimens.[20,21]

Results

Study selection

A total of 165 full-length articles were assessed for eligibility (Figure 1). Of these, 36 studies were considered eligible for

Table 2 Characteristics of studies with patients in the one-stage revision cohort

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Gender, % male	Age, years (range)	Time with infection/ infected prosthesis
Yoo et al[47]	Cementless	12	1991–2005	67	50 (29–72)	3.6 years (1.2–9.8)
Lai et al[48]	Cementless	7	1991–1993	71	62 (52–68)	"Late or delayed"
Rudelli et al[49]	Cementless	6	1989–1994	50	60 (39–71)	Minimum 4 months
Mulcahy et al[50]	Cemented	15	n/a	87	64 (49–82)	2.2 years (6 months–16 years)
Callaghan et al[51]	Cemented	24	1977–1983	50	65 (37–86)	4.9 years (1–11)
Hope et al[52]	Cemented	72	1976–1987	44	64 (30–85)	n/a (>3 weeks after pre-op aspiration)
Ure et al[53]	Cemented	20	1979–1990	80	61 (32–85)	53 months (6.6–148)
Raut et al[54]	Cemented	183	1979–1990	52	65 (17–84)	n/a (referalls)
Drancourt et al[55]	Cemented	10	1987–1991	n/a	n/a	32.6 months (1–130)
Rudelli et al[49]	Cemented	26	1991–2000	38	62 (37–83)	minimum 4 months

inclusion in the review. Of the 36 included studies, 31 (86%) were identified by the electronic-database search. The World Health Organization search revealed one relevant ongoing trial (Cementless One-Stage Revision of the Chronic Infected Hip Arthroplasty; NCT01015365). No relevant completed or terminated trials were registered. The search of the Cochrane Library revealed no further relevant studies. The cross-referenced reviews were acquired as part of background research.[8,9,14,15,18,24–46]

Description of included studies

Study characteristics are summarized in Tables 2 and 3. The patients in the 36 included studies were divided into two cohorts of distinctly separate revision strategies: a one-stage-revision cohort (Table 2) comprising relevant patients from ten studies (n = 375 [cementless reimplantation, n = 25 patients;[47–49] cemented reimplantation, n = 350 patients[49–55]]) and a two-stage-revision cohort (Table 3) comprising relevant patients from 28 studies (n = 929 [cementless reimplantation, n = 189 patients;[48,56–62] cemented reimplantation, n = 177 patients;[63–69] no specific information on type of reimplantation at patient level, n = 563 patients[11,13,16,70–78]]). Gender and age did not differ between the cohorts based on the available data. In the one-stage cohort, 195 of 365 (53.4%) patients were male, compared to 400 of 699 (57.2%) patients in the two-stage cohort, although 230 of 929 (24.8%) patients in the two-stage cohort had no data on gender, compared to ten of 375 patients in the one-stage cohort. The reported average age in the one-stage cohort was 61.4 years, compared to 63.1 years in the two-stage cohort. Data on comorbidity on a patient level or for the study cohort as a whole were only available in 14 studies (in only one of ten studies with patients in the one-stage cohort, compared to 14 of 28 studies with patients in the two-stage cohort). Thirteen of the 36 studies originated from North America, eleven from Europe, nine from Asia/Australia and three from South America. In the one-stage cohort, 280 of 375 (75.0%) patients originated from European studies, as did 261 of 929 (28.1%) in the two-stage cohort. In contrast, only 44 of 375 (11.7%) patients in the one-stage cohort and 445 of 929 (48.0%) patients in the two-stage cohort originated from North American studies. The one-stage cohort studies tended to be older: six of ten studies were published in the period 1990–1999 and three of ten studies were published after 1999, whereas in the two-stage cohort seven of 28 studies were published in the period 1990–1999 and 20 of 28 studies after 1999. Regarding the methodology of the included studies, we found no comparative studies that compared patients exposed to one-stage revision with a concurrent or historical control group of patients with two-stage

Antibiotic treatment regime (study level)	Non-septic revisions after reimplantation, n (%)	Follow-up, month (range)	Definition of infection (study level)
iv or iv/po combined for 3–24 weeks	1 (8)	86,4 (39,6–135,6)	Chronic hip pain + purulent fluid/pus on op + elevated crp or SR (a positive culture to be included in study)
iv 2–6 weeks then po min 2 months	n/a	42 (33–54)	Positive culture
iv min 4 weeks then po, total 6 months	0	138.7 (101–173)	A positive culture from min 6 samples (2 pt only fistula, 1 pt. Only pos culture from pre-op aspiration)
iv 3 weeks	0	48 (24–84)	Positive culture
iv 10 days then po 3–6 months	1 (4)	109,2 (12–168)	Positive culture + purulence/inflammation during opertion
n/a	2 (3)	45 (5–121)	"Clinical, hematological and radiological criteria" (in study only CNS proven infections)
iv 2–18 weeks then po 3–6 months	2 (10)	123,6 (66–205,2)	A positive culture + >5 polymorph leukocytes per field
iv 1–4 weeks then po 6 weeks–3 months	4 (2)	83 (24–164)	Pyogenic granulation tissue or pus or sinus + radiologic evidence + bacteriology
po 5 months before and 1 month after revision	n/a	27,6 (9–61)	Fistula or pain and elevated crp and SR > 50 or radiological loosening and elevated crp and SR > 50 AND 2 positive cultures
iv min 4 weeks then po, total 6 months	0	84,1 (42–175)	A positive cultures from min 6 samples (2 pt only fistula, 1 pt. Only pos culture from pre-op aspiration)

Abbreviations: n/a, not available; iv, intraveneous; po, per os; crp, c-reactive protein; SR, sedimentation rate.

Table 3 Characteristics of studies with patients in the two-stage-revision cohort

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Time with infection/ infected prosthesis	Gender, % male	Age, years (range)	Interval between first revison and reimplantation (range)
Lai et al[48]	Cementless	19	1991–1993	"late or delayed"	89	49 (29–67)	32,5 weeks (8–66)
Buttaro et al[56]	Cementless	29	1997–2000	11.7 months (3–48)	40	59 (32–78)	14.7 weeks (5–96)
Fehring et al[57]	Cementless	22	n/a	"Chronic infections"	n/a	n/a	4,7 months
Fink et al[58]	Cementless	36	2002–2006	4,4 years (±4 years)	44	69 (sd ±10)	6 weeks for all
Hofmann et al[59]	Cementless	27	1991–2001	63 months (2–413)	56	64 (38–87)	14 weeks (3–49)
Koo et al[60]	Cementless	12	1993–1997	8.25 months (2–36)	75	56 (37–73)	6 (6–8)
Yamamoto et al[61]	Cementless	10	1998–2002	48 days (32–73)	50	63 (44–76)	125 days (85–245)
Nestor et al[62]	Cementless	34	1984–1989	24 months, (1–108)	n/a	61 (26–70)	7 months (3–19)
McDonald et al[63]	Cemented	81	1969–1985	2,5 years (31 days–14,8 years)	53	60 (33–80)	1.5 years (6 days–6.2 years)
Cordero-Ampuero et al[64]	Cemented	20	1997–2007	>3 months since index surgery	40	67 (46–80)	9,1 months (3–23)
Evans[65]	Cemented	11	1995–2002	MSIS stage III	55	70 (43–90)	98 days (44–192)
Magnan et al[66]	Cemented	8	1996–1999	2–168 months	75	71 (58–83)	5 months (3–9)
Dairaku et al[67]	Cemented	7	n/a	50 months (2–103) (duration of infection before revision 1–12 months)	29	65 (55–81)	15 weeks (12–22)
Nusem and Morgan[68]	Cemented	18	1990–1999	6 years (2–10)	n/a	66 (45–86)	5 months (1–8)
Lieberman et al[69]	Cemented	32	1985–1988	41 months (1–186)	n/a	67 (32–89)	62 days (20 days–32 months)
Sanchez-Sotelo et al[70]	Unknown	168	1988–1998	5,1 year (4 months–20 years)	65	67 (32–89)	9,4 months (3–18)
Stockley et al[71]	Unknown	114	1991–2004	"Chronic infections"	55	64 (28–83)	6,4 months (2–22)
Hanssen and Osmon[13]	Unknown	17	1996–1997	26 months (1.4–28) (duration of infection MCPherson stage III)	47	64 (31–82)	159 days (90–780)

Spacer (with antibiotics)/beads/none	Antibiotic treatment regimen (study level)	Non-septic revisions after reimplantation, n (%)	Follow-up, month (range)	Definition of infection (study level)
Beads only 19 patients	iv 2–6 weeks then po min 2 months	n/a	38 (25–51)	Positive culture
None	iv 5–8 weeks then po 4–16 weeks	1 (3)	32.4 (24–60)	A positive culture from five samples
Beads only 16 patients	iv 6 weeks	1 (5)	37,5 (24–98)	A positive culture or positive histology for infection
Spacer (w)	iv 2 weeks then po 4 weeks	0	35 (24–60)	Pre-op hip aspiration and observation of the same microorganism in at least two of five cultures and observation of a microorganism in at least one sample and at least five neutrophilic polymorphonuclear leukocytes per high-power field (×400) in the associated histologic preparation
Spacer (w)	iv 6–8 weeks then for 17 pt po for 6 weeks	n/a	76 (28–148)	A positive culture or clinical history + elevated CBS, CRP, ESR + inflammation on frozen section
	iv 6 weeks	0	45 (24–66)	Positive culture or pus
Spacer (w)	iv 2–12 months	n/a	42.6 (5–62)	"Infection"
None	iv 28 days (9–42) then po 14 days (0–40)	2 (6)	47 (24–72)	Combination of pain, draining sinus, fever, haematolgical markers, scintigraphic scans, pre-op aspiration with positive cultures OR positive intraoperative cultures
None	iv 26 days (4–59) (two pt received oral instead). No antibiotics in cement	7 (9)	66 (24–163, 2)	Histological evidence of infection and positive culture or gross purulence
None	iv < 5 days then po 6 months	n/a	55,2 (12–132)	3 or more positive cultures
Spacer (w)	iv 6 weeks	0	24 (24)	"Infection" (10 culture positive, 1 culture negative)
Spacer (w)	n/a	0	36 (24–48)	"Infection" (4 culture positive, 4 culture negative)
Spacer (w)	n/a	1 (14)	18 (6–68)	Culture postitive (1 pt elevated crp + osteolysis)
Spacer (w)	iv 3–4 weeks then po 1–31 weeks	2 (11)	108 (60–168)	"Infection" (all patients seemingly culture positive)
Beads 4 patients	iv 41 days (20–49). Antibiotics in cement in only 17 pt	0	40 (24–75)	Culture positive
Spacer (w) 31 patients	iv 6 weeks (3–18)	34 (20)	24 (n/a–192)	Two or more positive cultures (n = 146) OR culture from pre-op aspiration with preoperative signs of infection: "frank pus", histopathologic exam, sinus
Beads	iv only 1. Postoperative day	n/a	74 (2–175)	Culture positive
None	n/a	n/a	n/a	Culture positive

(*Continued*)

Table 3 (*Continued*)

Authors	Reimplantation performed	Patients with performed reimplantation	Years of inclusion	Time with infection/ infected prosthesis	Gender, % male	Age, years (range)	Interval between first revison and reimplantation (range)
Incavo et al[72]	Unknown	11	n/a	47 months (3–240)	n/a	n/a	n/a (6–24weeks)
Takigami et al[78]	Unknown	8	1999–2006	18,6 months (1–56)	75	65 (49–79)	16,8 weeks (12–27)
Lim et al[73]	Unknown	34	1995–2006	41 months (2–144)	n/a	59 (35–79)	20 weeks (6–88)
Tsukayama et al[11]	Unknown	34	1980–1991	">one month after index op and had an insidious course"	n/a	n/a	110 days (34–720)
Wang et al[74]	Unknown	22	1988–1993	4,6 years (4 months – 11 years)	82	48 (28–75)	6,6 months (1,5–24)
Whittaker et al[75]	Unknown	43	1998–2003	12 months (3–36)	49	69 (33–90)	21 weeks (8 weeks–23 months)
Cabrita et al[16]	Unknown	55	1996–2003	>4 weeks	n/a	n/a	n/a (60–610 days)
Isiklar et al[79]	Unknown	9	1996–1998	28 months (3–96) (duration of infection > 6 weeks)	33	63 (38–78)	7 weeks (3–14)
Scharfenberger et al[80]	Unknown	8	1998–2003	>2 months	n/a	n/a	n/a
Walter et al[77]	Unknown	40	2001–2005	> 4 weeks	55	66 (48–86)	n/a

revision, or vice versa. One study was a randomized trial of spacer versus no-spacer treatment in patients who had all had two-stage revision.[16] Another study was a case-control study in patients with performed two-stage revision had become infected with resistant versus nonresistant microorganisms.[73] One study used cohort-outcome analysis to examine predictors of reinfection.[63] The remaining 33 of the 36 (92%) studies were purely descriptive case series of infected HA patients treated with one-stage or two-stage revision, reporting patient characteristics and frequencies of different outcomes, including reinfection. Twenty-eight of 36 (78%) studies used retrospective data collection. Only two studies described a priori defined primary end points. Three studies stated a study hypothesis, and 14 studies provided some degree of background information on in- and exclusion criteria for enrollment in the study. Eighteen studies did not report on the status of the infected index HA (being a primary/revision or cemented/cementless prosthesis). Fifteen studies evaluated the revision procedure by means of the Harris hip score.[11,16,47,48,50,57–59,61,64,68–70,77,79] Twelve studies did not use a standardized scoring system in evaluating patients postoperatively.[13,51,52,55,60,63,65,66,71–73,80] Four studies used the Merle d'Aubigné–Postel score.[49,54,56,75] The remaining five studies used other scoring systems.[53,62,67,74,78] Methodological characteristics of the included studies are shown in Table 4. In conclusion, methodological quality was considered low for most included studies, and we found no comparative studies examining one-stage versus two-stage revision.

Meta-analysis

We pooled data from 36 studies with a total of 1304 patients having a completed one-stage or two-stage revision and 126 registered reinfections following the reimplantation. Sensitivity analysis did not detect outliers, nor did it indicate that any estimate was heavily determined by a particular study. We found that reinfections for all studies occurred with an estimated risk of 11.3% (95% confidence interval [CI]: 9.6%–13.2%) (Figure 2). Reinfection occurred with an estimated risk of 13.1% (95% CI: 10.0%–17.1%) in

Spacer (with antibiotics)/beads/none	Antibiotic treatment regimen (study level)	Non-septic revisions after reimplation, n (%)	Follow-up, month (range)	Definition of infection (study level)
Spacer (w)	iv 4–6 weeks (then "some" patients po)	n/a	n/a	Culture positive
Ceramics blocks (w)	iv 4.2 weeks (2–8)	0	49 (24–81)	"… based on clinical, radiological and histological evidence …" – 6 pt culture positive
Spacer (w) or beads	iv 9.6 weeks (4–24)	2 (6)	52,8 (24–120)	2 or more positive culture OR histopathological exam OR sinus
Beads (w)	iv 6 weeks	n/a	50,4 (15,6–132)	Min 2 of 5 positive cultures OR pus preoperatively
Beads 13 patients	iv 16 days (7–42)	3 (9)	48 (24–84)	Preoperative pus or histopathological exam (all patients culture positive)
Spacer (w)	iv 2 weeks	0	49 (25–83)	2 or more positive cultures or histopathological exam
Spacer (w) 33 patients	iv 3 weeks then po 6 months	6 (11)	48 (24–102)	Culture positive
Spacer (w)	iv 3–14 weeks then po 12–24 weeks	0	24 (160–36)	S. Epidermidis proven infection
Spacer (w)	iv 6 weeks	1 (13)	n/a (24–n/a)	Culture positive
Beads or spacer (w)	Min 6 weeks, of iv + po	4 (10)	7 (3–48)	Culture positive

Abbreviations: n/a, not available; iv, intraveneous; po, per os; crp, c-reactive protein; SR, sedimentation rate.

the one-stage cohort and with an estimated risk of 10.4% (95% CI: 8.5%–12.7%) in the two-stage cohort (Figure 3). In the two-stage cohort, cementless reimplantation yielded a reinfection risk of 8.6% (95% CI: 4.9%–14.7%), and cemented reimplantation a reinfection risk of 12.3% (95% CI: 8.0%–18.4%) (Figure 4). In the one-stage cohort, only very limited data were available for cementless reimplantation (a total of just 25 cases). Meta-regression showed no correlation between study size and risk of reinfection pooling all studies ($\beta = 0.002$, $P = 0.172$) or within the two-stage cohort ($\beta = -0.002$, $P = 0.486$). However, within the one-stage cohort, a larger study size correlated with a higher risk of reinfection ($\beta = 0.005$, $P = 0.048$). Further exploration showed that the single study by Raut et al[54] had a considerable role in this correlation, with a relative weight of 62% in the one-stage group; however, this was not detected as statistically significant by sensitivity analysis. Meta-regression indicated that a more recent publication pooling all studies correlated with a lower risk of reinfection ($\beta = -0.029$, $P = 0.020$), but no correlation could be identified when stratified (one-stage cohort: $\beta = -0.032$, $P = 0.346$; two-stage cohort: $\beta = -0.026$, $P = 0.098$). Graphical evaluation of funnel plots confirmed the likely presence of missing smaller studies with higher reinfection risk.

Discussion

Summary of evidence

The results of this meta-analysis suggest the presence of nearly three additional reinfections per 100 reimplanted patients when performing a one-stage revision compared to a two-stage revision strategy for treatment of chronic infection in HA. However, we believe it is difficult to draw any conclusions on the superiority of either revision strategy from the available data. Even with the reasonably large number of studies, the pooled reinfection-risk estimates were statistically imprecise, with overlapping confidence intervals. Furthermore, one must consider that these risk estimates are based purely on data from case series with limited information on potential confounding factors. No single study has directly compared the two revision strategies. Also, the different

Table 4 Methodological characteristics of included studies

Authors	Study design	Comparing cohorts of 1- vs 2-stage revision	Data collection	In-/exclusion clearly defined	Co-morbidity defined or includeded patients (study or patient level)	Follow-up more than 2 years for all patients	Patient level information regarding microbial diagNosis and antibiotic treatment regimen	Number of urgeons performing there visions	Information on nature of infected index prosthesis
Yoo et al[47]	Cohort	No	Retrospective	Yes	No	Yes	No	Yes	Yes
Lai et al[48]	Cohort	No	Retrospective	No	Yes	Yes	No	Yes	Yes
Rudelli et al[49]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Mulcahy et al[50]	Cohort	No	Retrospective	No	No	Yes	No	Yes	No
Callaghan et al[51]	Cohort	No	Retrospective	Yes	No	No	No	No	Yes
Hope et al[52]	Cohort	No	Retrospective	Yes	No	No	No	Yes	Yes
Ure et al[53]	Cohort	No	Prospective	No	No	Yes	Yes	No	No
Raut et al[54]	Cohort	No	Prospective	No	No	Yes	No	Yes	Yes
Drancourt et al[55]	Cohort	No	Prospective	Yes	No	Not	Yes	No	No
Buttaro et al[56]	Cohort	No	Retrospective	Yes	No	Yes	No	No	Yes
Fehring et al[57]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Fink et al[58]	Cohort	No	Prospective	Yes	Yes	Yes	No	No	Yes
Hofmann et al[59]	Cohort	No	Retrospective	No	No	Yes	No	Yes	Yes
Koo et al[60]	Cohort	No	Retrospective	No	No	Yes	Yes	No	Yes
Yamamoto et al[61]	Cohort	No	Retrospective	No	Yes	No	No	No	Yes
Nestor et al[62]	Cohort	No	Retrospective	No	No	Yes	Yes	Yes	Yes
McDonald et al[63]	Cohort	No	Retrospective	No	No	Yes	No	No	Yes
Cordero-Ampureo et al[64]	Cohort	No	Prospective	Yes	No	No	Yes	No	No
Evans[65]	Cohort	No	Retrospective	No	Yes	Yes	Yes	No	No
Magnan et al[66]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Dairaku et al[67]	Cohort	No	Retrospective	No	No	No	Yes	No	Yes
Nusem and Morgan[68]	Cohort	No	Retrospective	No	No	Yes	No	No	No
Lieberman et al[69]	Cohort	No	Retrospective	Yes	No	Yes	No	No	No
Sanchez-Sotelo et al[70]	Cohort	No	Retrospective	Yes	Yes	Yes	No	No	Yes
Stockly et al[71]	Cohort	No	Prospective	No	No	No	No	Yes	No
Hanssen and Osmon[13]	Cohort	No	Retrospective	No	Yes	No	No	Yes	Yes
Incavo et al[72]	Cohort	No	Retrospective	No	Yes	No	No	No	Yes
Takigami et al[78]	Cohort	No	Retrospective	No	No	Yes	Yes	No	No
Lim et al[73]	case-control (-on sensitivity pattern)	No	Retrospective	Yes	Yes	Yes	No	Yes	No
Tsukayama et al[11]	Cohort	No	Retrospective	No	No	No	No	No	Yes
Wang and Chen[74]	Cohort	No	Retrospective	No	Yes	Yes	No	No	Yes
Whittaker et al[75]	Cohort	No	Prospective	Yes	Yes	Yes	No	No	No

Cabrita et al[16]	RCT (spacer vs no spacer)	No	Prospective	Yes	Yes	No	No	No	No	No
Isiklar et al[79]	Cohort	No	Prospective	Yes	Yes	No	Yes	No	No	No
Scharfenberger et al[80]	Cohort	No	Retrospective	Yes	Yes	Yes	No	No	No	No
Walter et al[77]	Cohort	No	Prospective	No	Yes	No	No	No	No	No

clinical settings and patients underlying the two revision strategies must be taken into account. Nevertheless, we have demonstrated the lack of clear evidence proving one-stage revision to be a less effective treatment strategy for chronic infections in HA, as has been previously claimed.[18]

Strengths and limitations

The data presented in this review are the best available at present to clinicians worldwide, and have so far been used to advocate the different treatment strategies offered.[9,18] We quantified these data for the first time in a systematic review and meta-analysis. Yet it became apparent that neither controlled clinical trials nor observational studies have directly compared one-stage and two-stage revision for treatment of chronic infections in HA. The estimates obtained in this review are obtained from a wide diversity of patients, the majority of studies were small and based on retrospective data collection, and results from the two cohorts should be compared with great caution. Due to the unavailability of confounding factors in many of the studies, we chose simply to estimate pooled absolute risks of reinfection in the two cohorts, rather than a risk-ratio estimate in a direct comparison, as we had no way to control for potentially skewed distribution of covariates. Ignoring this would in our opinion compromise the entire study. We thus believe the reported absolute estimate gives a fair opportunity for better understanding the conclusions drawn from this review.[81] Yet several aspects must be emphasized.

Terminology

Infection in HA is by far the most difficult area to define, as this is often covered by a multitude of overlapping symptoms and clinical findings, which added together strongly indicate a septic complication. Even the gold standard in diagnosing infection – perioperative cultures – is not absolute. Culture-negative patients may still be infected, and single- or even double-positive culture may represent contamination.[82,83] Several different definitions of infection have been used in the included studies (Tables 2 and 3). We chose a pragmatic approach for our review, and defined the presence of infection as defined by the authors of the individual study. However, as the definition of infection and reinfection in the 36 included studies varied considerably, ranging from "infection"/clinical features of infection to obtainment of positive bacterial cultures, the risk of misclassification is inherent. For example, patients with aseptic loosening may have been misclassified as reinfected, whereas patients with true infection who did not undergo reoperation after revision may have been missed.

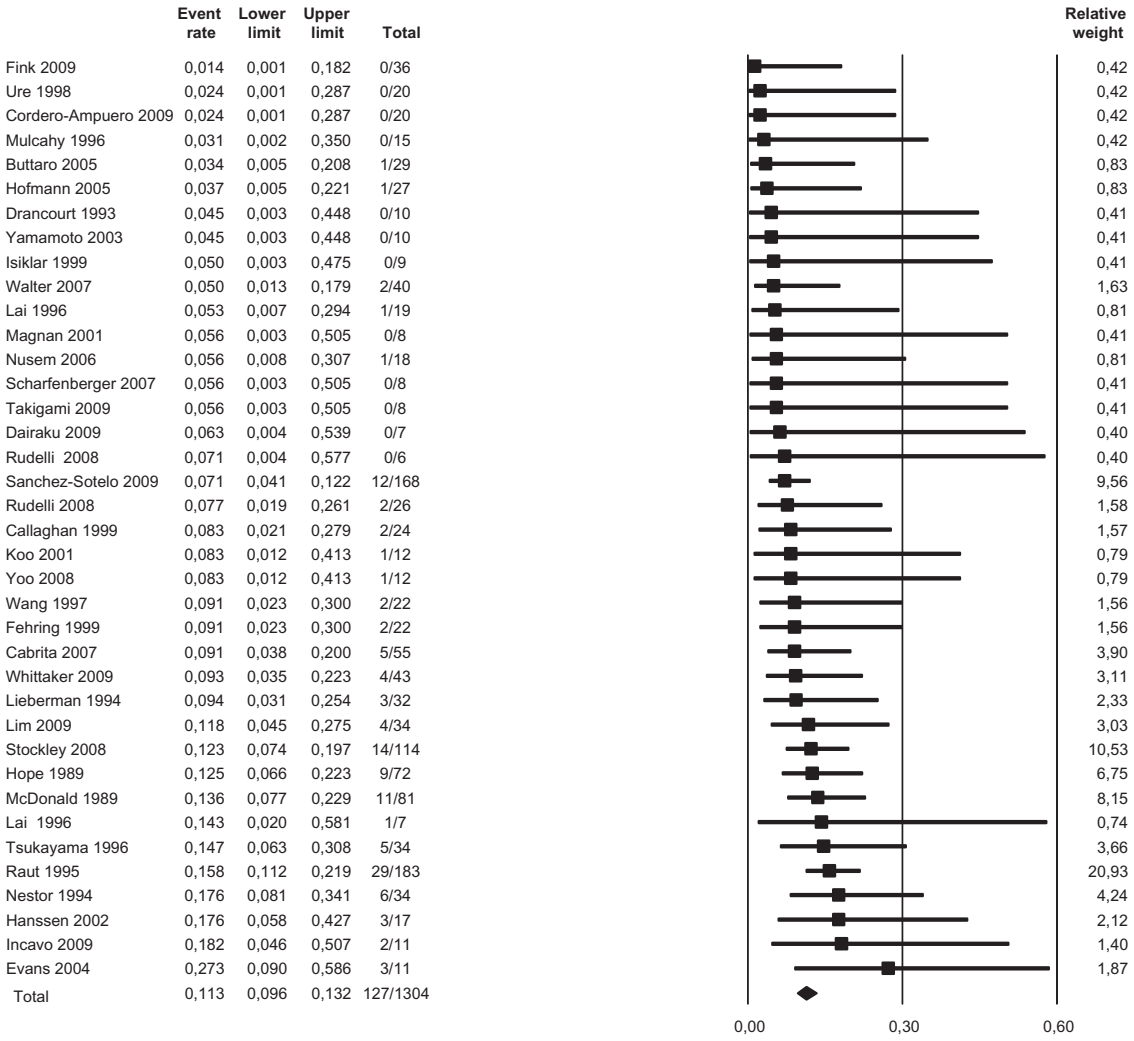

Figure 2 Forest plot illustrating absolute risk of reinfection in ascending order with relative weight of individual studies.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.

Many definitions of "chronic infection" exist.[8,11,13,29,45,84–86,87] A priori, we aimed to define chronic infections according to McPherson, as infections with a duration of symptoms above 4 weeks, regardless of origin.[88] This has also been advocated by others as the best definition at present and has been used recently, in studies of arthroplasty infections and HA studies in particular, by multiple international orthopaedic centers.[13,26,77,89–91] However, during study selection, it became apparent that the definition by McPherson[88] was very difficult to apply to the existing literature, as many studies reported only the interval from last operation to subsequent revision or from last operation to diagnosis of infection. Subsequently, we also chose to include studies that defined chronic infections as more than 1 month since last surgery, regardless of symptom duration, and by authors stating an infection as chronic (Tables 2 and 3).[11] If no data were available regarding these time limits, the study or patients were not included in our review. Thus we may have included patients with acute hematogenous infections, and we may have excluded potentially eligible patients from our analysis. A very strict definition of chronic infection at patient level is thus an element not taken into account in this analysis, as these data were not available to the authors.

Risk-factor assessment

Many apparent risk factors have been suggested to predict worse outcomes when treating infected hip arthroplasties, but few have been validated and the quality of evidence is poor.[5] Concerning the present study, 60% of studies in the one-stage cohort were published in the period 1990–1999, while 71% of studies in the two-stage cohort were published after 1999. A generally decreased risk of reinfection over time may have

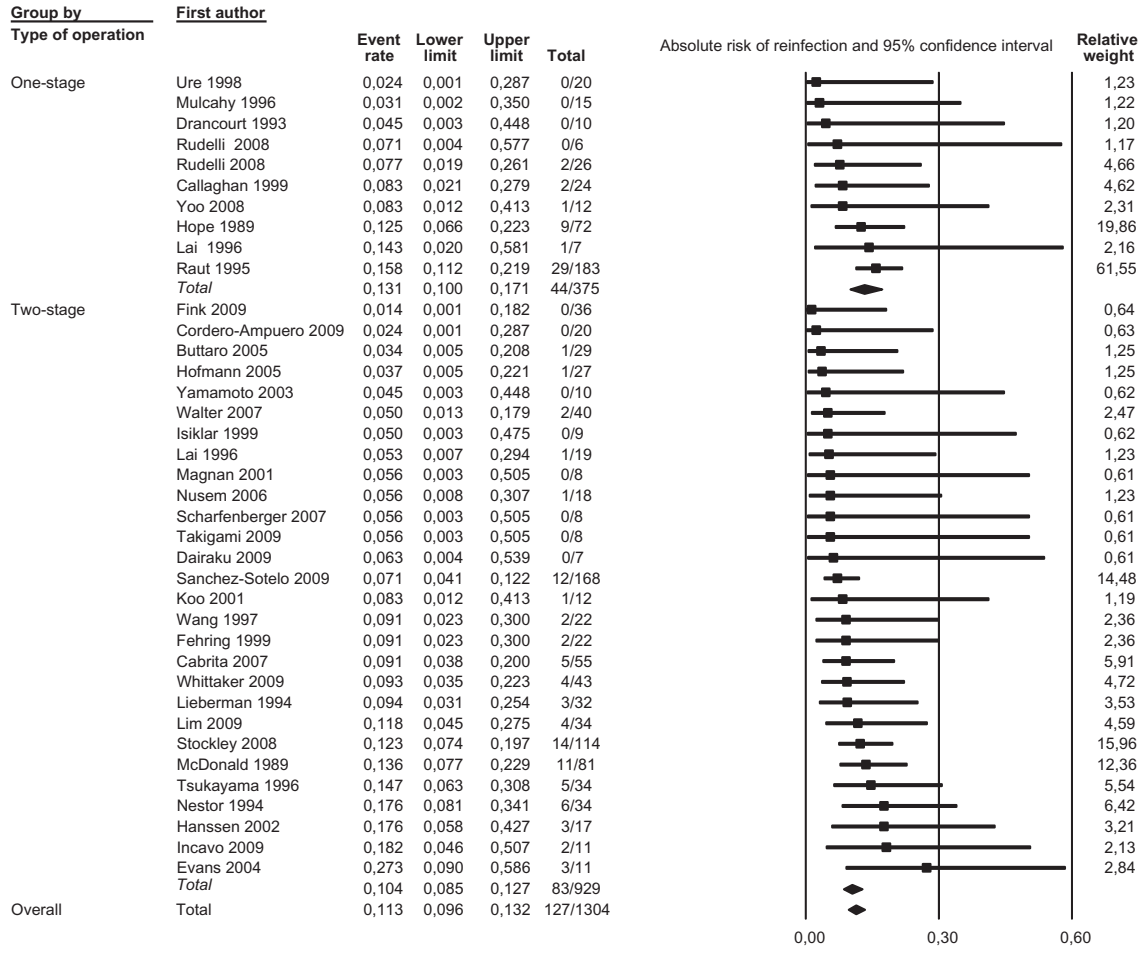

Figure 3 Forest plot illustrating stratified analysis by type of revision performed with relative weight of individual studies.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.

led to an overestimation of the reinfection risk associated with one-stage procedures conducted many years ago. As our understanding of the importance of many different treatment aspects increases over time, so may our overall results improve, regardless of the chosen surgical strategy. The articles from which data are analyzed span more than two decades; surgical techniques and materials used have evolved, as well as general knowledge on infections and patient care. Undoubtedly, better knowledge of optimal antibiotic therapy in prophylactic and active treatment, eg, the use of antibiotic-enriched cement and differences in local resistance patterns, but also the emergence of multiresistant organisms, could have influenced the reinfection risk over time. Improved understanding of biofilm-producing microorganisms is

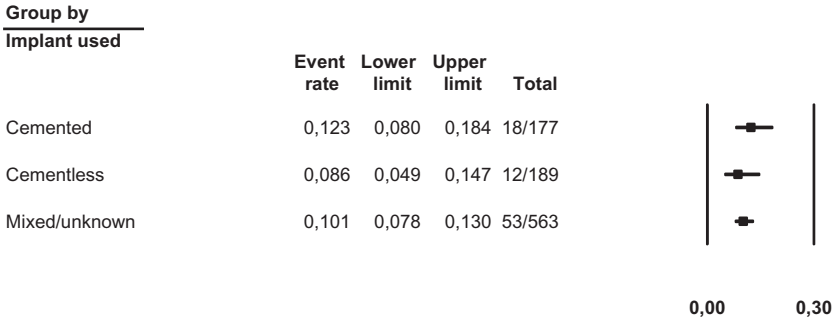

Figure 4 Forest plot illustrating two-stage revision stratified by implant used in reimplantation.
Notes: Event rate, absolute risk of reinfection; lower/upper limits, 95% confidence interval; total, number reinfected/number reimplanted.
Abbreviation: CI, confidence interval.

essential in today's aggressive debridement approach, recognizing the need for absolute removal of dead matter and foreign materials. Our review does not take these important developments over time into account, as good data on these risk factors do not exist in the present studies. Comorbidity, high American Society of Anesthesiologists score, long duration of the surgical procedure, and low hospital and surgeon volume have been suggested as important risk factors for reinfection.[5] In contrast, gender or increased age apparently do not constitute important risk factors, but data quality is poor and conflicting evidence exists.[5,92] Age and gender were also quite evenly distributed in the one-stage and two-stage cohorts in this review. Explicit data on comorbidity at a patient level or even just study level is absent from most studies, as only 14 of 36 studies reported this data. In our opinion, the apparent large difference in reported patient comorbidity (10% among one-stage studies versus 50% among two-stage studies) is most likely due to underreporting, not ignoring that a possible genuine lower comorbidity in the one-stage cohort on the other hand may have led to an underestimation of the reinfection risk associated with this procedure. Furthermore, certain types of medication may directly constitute risk factors, including treatment with bisphosphonates.[93] However, information on medical treatment of the included study populations is not available. The chosen antibiotic treatment strategy is an area of specific interest regarding reinfection, as the surgical procedure by itself does not resolve the infection. Furthermore, the nature of the infecting microorganism may be a key element regarding outcome. Thus, Gram-negative organisms, multiresistant organisms, and polymicrobial infections have been proposed to predict worse outcomes. As shown in Tables 3 and 4, this information is not readily available in the existing studies to a degree at which we could adjust for any differences in these and other risk factors in our meta-analysis.

Potential bias

Whether to choose a specific surgical intervention in a non-research, everyday clinical practice environment is determined by many factors. This raises the concern of whether the selection of patients in the individual 36 studies is alike, with consequences for the comparability of the two cohorts in this review. As noted above, a potentially skewed distribution of unreported or unknown confounders may exist. Confounding by indication (surgical bias) could potentially influence the results obtained in this analysis, as surgeons may choose less severely ill patients (eg, with known nonresistant microorganisms) for one-stage revision. By the very nature of two-stage surgery, the surgeon is able to evaluate the progress before reimplantation, this being one of the clinical strengths of this approach compared with one-stage revision. The exclusion in our meta-analysis of patients for whom the second stage was not completed may favor the two-stage approach, since the patients who did not undergo the second stage may constitute a group with poor outcomes. Finally, by limiting our search to English- and German-language studies from only two electronic databases, we may have overlooked studies published in nonindexed journals, or data presented at national or international conferences, which most likely would include more unfavorable results.

Implications for future research

We believe that complications and outcomes (including validated patient-related outcomes measures) of the different revision strategies need more research attention. Recently, the proportion of complications with interim-spacer application has been reported as high as 60%, and fatal complications have also been reported.[16,91] Appropriate patient selection seems to be a crucial aspect of success.[15,40,94] Given the complexity and relative scarcity of patients with chronically infected HA, randomized clinical trials may prove difficult to perform. The estimates obtained in our analysis suggest that a sample size of more than 3500 infected patients would be needed to investigate superiority of two-stage versus one-stage revision regarding reinfection with statistical precision. Meanwhile, we recommend adoption of standardized reporting of essential data among patients treated for chronically infected HA to ensure the future possibility of performing improved collaborative meta-analysis.[21] We thus recommend that future publications on this matter include relevant individual patient information, making it possible to pool data on a patient level, including detailed data on potential risk factors, duration since last surgical procedure, the duration of symptoms, clear information regarding diagnosis of infection, and grade according to the modified McPherson staging system.[13]

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Disclosures

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Chronic Infected Hip Arthroplasty trial. No other conflict of interest exists for any of the authors.

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