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ESPS Peer-review Report
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[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
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		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS
Poorly written.

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ESPS Peer-review Report
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[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

Thank you for giving me the opportunity to review the manuscript entitled "Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? A systematic literature review". Here are my comments. ABSTRACT I do believe that systematic review has to include search of at least two data bases. As only one base was searched here (PubMed), this cannot be a systematic review. Results: I find presented percentages (21%; 75%; 70.4%; 92.8 %; and 89.6%) confusing there. That requires additional explanation. KEY WORDS Why were the terms "irrigation" and "retention" left out from the key words list? The terms were used to search the PubMed base. MATERIALS AND METHODS If the abbreviation is DAIR, wouldn't it be expected to have order "Debridement, Antibiotics, Irrigation, and Retention" instead of "Debridement, Irrigation, Antibiotics, and Retention"? As I am curious, could the author explain me why the studies with <10 patients were excluded from the review? DISCUSSION The first paragraph of the discussion has to present the main finding of the study. It was not the case here. Again, this review cannot be attributed as a systematic one. The authors have concluded that the present literature review shows that debridement, irrigation, antibiotic therapy, and prosthesis retention is an acceptable solution in the management of early and acute hematogenous periprosthetic hip joint infections. Where was the change of modular prosthesis components lost?!

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[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
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COMMENTS TO AUTHORS
Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? A systematic literature review

Running title: Hip joint infections and prosthesis retention

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Abstract

Aim:

To systematically evaluate the current literature about how successfully periprosthetic hip joint infections can be managed by debridement and prosthesis retention

Methods:

A literature search was performed through PubMed until September 2013. Search terms were "DAIR (debridement, irrigation, antibiotics, and retention)" alone and in combination with "hip" as well as "hip infection + prosthesis retention".

Results:

A total of 11 studies reporting on 292 cases could be identified. Five different treatment modalities have been described with varying success rates (debridement – 21 %; debridement + lavage – 75 %; debridement, lavage, with change of modular prosthesis components – 70.4 %; debridement, lavage, change of modular prosthesis components + vacuum-assisted closure – 92.8 %; acetabular cup removal + spacer head onto retained stem – 89.6 %). With regard to the postoperative antibiotic therapy, no general consensus could be drawn from the available data

Conclusion:

Debridement, irrigation, antibiotic therapy, and prosthesis retention is an acceptable solution in the management of early and acute hematogenous periprosthetic hip joint infections. The current literature does not allow for generalization of conclusions with regard to the best treatment modality. A large, multi-center study is required for identification of the optimal treatment of these infections.

Keywords: hip joint infection, prosthesis retention, debridement, hip revision, antibiotic therapy

Introduction

Despite numerous prophylactic measures infections still occur in 1-2 % after total hip arthroplasty (THA), whereas this rate may increase after revision surgery [1]. In the future, the overall infection rate is likely to increase as the life expectancy of the implants is increased and patients are followed up longer. Depending on the time of infection manifestation, duration of symptoms, virulence and antibiotic resistance profile of the pathogen organism, and the general medical condition of the patient, several treatment options are available including both one- and two-stage procedures [1].

Hip joint infections are actually categorized into early, delayed, and late infections [1]. Although these terms are widely accepted, a discrepancy regarding the precise differentiation of the time periods still exists. Some authors define early infections as those occurring within the first four [2-3] or six [1] postoperative weeks, whereas others propose the first three months to be the limit [4]. Similar to that, the definition of late infections vary from the period beyond the first four postoperative weeks [2-3] to beyond the first 24 postoperative months [4].

The correct definition of the joint infection with regard to the time of infection manifestation is important for making the correct decision about the ideal treatment procedure. Generally, it is accepted that early infections are likely to be successfully managed by debridement, lavage, and prosthesis retention, whereas late infections require prosthesis removal and one- or two-stage-reimplantation in order to achieve infection eradication [5]. However, the literature data about this topic cannot be always evaluated and compared to each other to a sufficient and reliable way due to inhomogenities in the treatment procedure, patients' collective, antibiotic therapy or length of follow-up.

Hence, the aim of the present study was to systematically evaluate the current

literature about how successfully periprosthetic hip joint infections can be managed by debridement and prosthesis retention.

Materials and Methods

A literature search was performed through PubMed until September 2013 (Fig. 1). Search terms were "DAIR (debridement, irrigation, antibiotics, and retention)" alone and in combination with "hip" as well as "hip infection + prosthesis retention". Only English studies were included. Reviews, case reports and case series with a number of patients < 10 were excluded from the study. Studies reporting about both hip and knee cases but not allowing for differentiation between the particular outcome were also excluded. From the identified studies, a search was carried through the bibliography of each article in order to identify further studies. All studies were analysed with regard to publication date, number of patients treated, type of infection, surgical treatment modalities, surgical complications, type and length of antibiotic therapy, follow-up, and level of evidence. Studies reporting only partly on these parameters were also excluded.

Results

A total of 11 studies reporting on 292 cases could be identified (Fig. 1) [2-3,6-14]. Two

studies were published before and nine after 2000. Two studies had a level of evidence III and nine level of evidence IV (Table 1).

Of the 292 cases, there were 216 early and 57 late infections (with a variable definition of early vs. late infection). The remaining 19 cases were acute hematogenous according to the criteria by Tsukayama et al. [2] (Table 1).

Regarding the treatment procedures, five different modalities have been described (Fig 2). One study [10] reported on debridement and another on debridement and irrigation [12]. Six studies performed debridement, lavage and change of modular prosthesis components (polyethylene (PE) liner, femoral stem head) [2-3,6-7,9,14], whereas in one of these studies the PE liner was not changed in all patients [9]. One study combined this procedure along with the use of the vacuum-assisted closure therapy [11]. Two studies reported on partial prosthesis retention [8,13]. In both studies, the infected acetabular cup was removed and an antibiotic-loaded spacer head was placed onto the retained femoral stem. Although it is difficult to evaluate the cumulative infection eradication rate for each procedure separately, literature data indicate a higher success rate for the two latter procedures (Fig. 2).

Complications beside persistence of infection or emergence of new infection included mostly prosthesis dislocations and aseptic prosthesis loosening (Table 2).

With regard to the postoperative antibiotic therapy, no general consensus could be drawn from the available data (Table 3). Some studies gave only intravenous antibiotics, whereas others combined intravenous and oral antibiotics. Similar discrepancies could be observed regarding the length of antibiotic therapy, which varied from four weeks to one year (Table 3).

All studies provided a mean follow-up of at least 24 months (Table 2). Depending on the salvage procedure used in each study, the infection eradication rate ranged from 21 % to beyond 90 % (Table 2).

Discussion

Periprosthetic joint infections (PJI) still remain a hazardous complication after primary and revision THA. A regimen of debridement, irrigation, prosthesis

retention, and antibiotic therapy is generally accepted for acute infections without complicating factors such as significant comorbidity, not intact soft tissues surrounding the prosthesis or loosening of the prosthesis [18]. The aim of the present review was to investigate whether it is possible to treat these infections by prosthesis retention.

To the best of our knowledge, our literature search revealed 11 relevant studies. Our strict inclusion criteria led to the exclusion of numerous studies which might have provided more information and allowed for a more reliable interpretation of the data. However, the purpose of the present study was to evaluate only studies reporting on hip joint infections. Several well-designed studies with a higher level of evidence report about DAIR including both THA and total knee arthroplasty (TKA) cases, whereas a differentiation of the results between both primary surgeries is not possible [15-28]. Similar to that, other studies present data only about small case series [29-31]. We represent the opinion that the proper identification of relevant studies is crucial when a systematic literature review is performed.

The findings of the present review indicate that the infection eradication rates with regard to prosthesis retention are lower compared to those reported after one- or two-stage revision surgery [5]. Although single studies demonstrated high success rate exceeding 90 %, the relative small number of patients treated as well as the low level of evidence does not allow for generalization of conclusions. Two possible causes might be responsible for this lower infection eradication rate: the low power of the included patients of the identified studies, and the patients' collectives themselves, which are different compared with those treated by one- or two-stage revision arthroplasty.

The present review identified five different treatment modalities for management of THA-PJIs with varying success rates. Especially older studies showed lower success rates compared to younger ones. This discrepancy might be possibly explained by advances in surgical and debridement techniques, use of pulsatile lavage or even antiseptic solutions as well as application of new and more potent antimicrobial

drugs. Moreover, some studies present some partly surprising results. Choi et al. retrospectively compared 28 cases having prosthesis retention with 65 cases having been treated by staged revision and identified risk factors for infection persistence [9]. Infection of revision THA, acute phase treatment (less than four weeks), and polybacterial infection were identified as independent predictors for failure of infection control after initial surgery. Additional subgroup analysis to identify other possible contributing factors identified no difference between methicillin-sensitive and methicillin-resistant staphylococcus or head/liner exchange and no exchange [9]. These findings are contradictory to the general acceptance that prosthesis retention is feasible at the site of early infection with a short duration of symptoms. Similar accounts for the non-significant difference between head/liner exchange and no exchange. Theoretically, the change of modular prosthesis components should reduce the bacterial load in the wound, and hence lead to better infection eradication rates.

The decision with regard to the ideal treatment procedure for management of PJIs of the hip joint is made based on several factors such as time of infection manifestation, duration of symptoms, local soft-tissue situation, number of prior surgeries, identification of pathogen organism, its virulence and antibiotic resistance profile as well as patient's comorbidities. Various risk factors have been described that are associated with occurrence of PJI, such as rheumatoid arthritis, diabetes mellitus, malignancy, obesity, and use of immunosuppressive drugs [15,20,32-34]. Revision surgery also increases the risk of PJI [17,33-34]. Factors that have been associated with a worse outcome of PJI treatment including both THA and TKA involve infections caused by Staphylococcus species [15], and more specifically by Staphylococcus aureus [17,35-37], polymicrobial PJI [20], intra-articular purulence [15], retention of exchangeable components [20], and longer time between initial arthroplasty and PJI diagnosis [16,20,36,38].

Despite the aforementioned known risk factors the ideal treatment procedure is difficult to choose due to the definition of the infection itself. Although several

classification systems have been proposed [1-4], the exact definition of an early vs. late periprosthetic infection still remains controversial. This distinguishment is essential since it is widely accepted that only early infections can be successfully treated by prosthesis retention. With regard to early as well as late infections the discrepancy between the several classification systems means that symptoms that are present for several weeks to months might not be ideally treated. The only point that all these systems agree for is the cause for the emergence of each infection [1]. Early infections are attributed to an intraoperative contamination [1]. Delayed or low-grade infections are also attributed to an intraoperative contamination, however an infection manifestation has not evolved due to a small bacteria number, low virulence of the causative organism or adverse local conditions for bacteria growth [1]. Late infections are hematogenously acquired, whereas in 20-40 % of the cases the primary infection source remains unidentified [1]. Practically, all these definitions are an attempt to separate surgically from nonsurgically acquired infections, and the problem is where to draw the line. Clearly, not every early infection is surgically acquired and not all late infections are from other sources [1].

Moreover, an unanswered question regards the insertion of antibiotic-loaded device (cement beads or collagen sponges) when DAIR is performed. To the best of our knowledge, the effect of antibiotic-impregnated beads at the site of DAIR has not been studied. The use of gentamicin-loaded collagen sponges has been described in a few studies in the treatment of PJI [39-41].

The optimal antibiotic treatment (the choice and duration) of PJIs is still unknown. Some authors recommend a duration of antibiotic treatment for 6 months for TKA-PJIs and 3 months for THA-PJIs when treated with DAIR [4]. In some recent studies, it has been reported that a shorter course of antibiotics might be also an alternative in DAIR treatment [21,23,28,37]. This confusion regarding the optimal duration of antibiotic therapy is also evident in the present literature review. Antibiotics were administered over different periods varying from four weeks to one year. Due to the relative small power of the included cases and inhomogenities in the

treatment procedures and collectives themselves it cannot be stated which antibiotic treatment is the optimal.

In conclusion, the present literature review shows that debridement, irrigation, antibiotic therapy, and prosthesis retention is an acceptable solution in the management of early and acute hematogenous periprosthetic hip joint infections. The current literature does not allow for generalization of conclusion with regard to the best treatment modality. A large, multi-center study is required for identification of the optimal treatment of these infections.

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Tables

Table 1: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to publication year, number of patients treated, type of infection, and level of evidence.

Study	Publication year	Number of patients	Type of infection	Level of evidence
Aboltins et al. [6]	2007	13	7 early 6 late	IV
Aboltins et al. [7]	2013	19	all early	III
Anagnostakos et al. [8]	2010	12	all late	IV
Choi et al. [9]	2012	28	all early	III
Crockarell et al. [10]	1998	42	19 early 19 late 4 acute hematogenous	IV
Kelm et al. [11]	2009	28	all early	IV
Kluche et al. [12]	2011	12	all early	IV
Lee et al. [13]	2013	19	10 late 9 acute hematogenous	IV
Tsukayama et al. [2]	1996	41	35 early 6 acute hematogenous	IV
Waagsbo et al. [3]	2009	40	30 early 10 late	IV
Westberg et al. [14]	2013	38	early	IV

Table 2: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to surgical treatment modalities, -complications, infection eradication rate, and length of follow-up.

Study	Surgical treatment procedure	Surgical complications	Infection eradication rate	Follow-up [months]
Aboltins et al. [6]	debridement, lavage, change of PE-liner (median=1 [1-4])	1/13 aseptic prosthesis loosening	92.3 %	42 [24-76]
Aboltins et al. [7]	debridement, lavage, change of PE-liner (median=3 [3-6])	n.c.d.	89.5 %	24 [15-37]
Anagnostakos et al. [8]	acetabular cup removal + spacer head onto retained stem mean implantation period 88 [35-270] days	2/12 draining sinus after spacer head implantation; 1/12 spacer dislocation; 3/12 prosthesis dislocation	91.6 %	55 [12-83]
Choi et al. [9]	19/28 debridement, irrigation, change of PE-liner 9/28 debridement, irrigation, no change of PE-liner	5/28 staged revision, 6/28 repeated debridement, 4/28 resection arthroplasty	50%	59 [20-110]
Crockarell et al. [10]	debridement	1/42 prosthesis dislocation, 1/42 periprosthetic femoral fracture, 1/42 exitus due to sepsis	21% *	76 [2-264]
Kelm et al. [11]	debridement, pulsatile lavage, change of PE-liner, vacuum-assisted closure (V.A.C.)	none	92.8 %	36 [12-87]
Kluche et al. [12]	debridement, irrigation change of PE-liner and femoral head	n.r.	75%	40 ± 23
Lee et al. [13]	acetabular cup removal +	n.r.	89.5 %	48 [24-96]

	spacer head onto retained stem			
Tsukayama et al. [2]	debridement, change of PE-liner	1/35 acetabular component loosening 2/6 acetabular component loosening	71 % (early) 50% (acute hematogenous)	40 [4-81] 31 [6-48]
Waagsbo et al. [3]	debridement + prosthesis retention	n.r.	67.5 %	49 [13-119]
Westberg et al. [14]	debridement, pulsatile lavage, change of modular prosthesis components	8/38 prosthesis dislocation	71%	48 [9-120]

PE: polyethylene; n.c.d. : not clearly described; n.r. not reported; *: 4/19 early successful, 2/4 acute hematogenous, 0/19 late

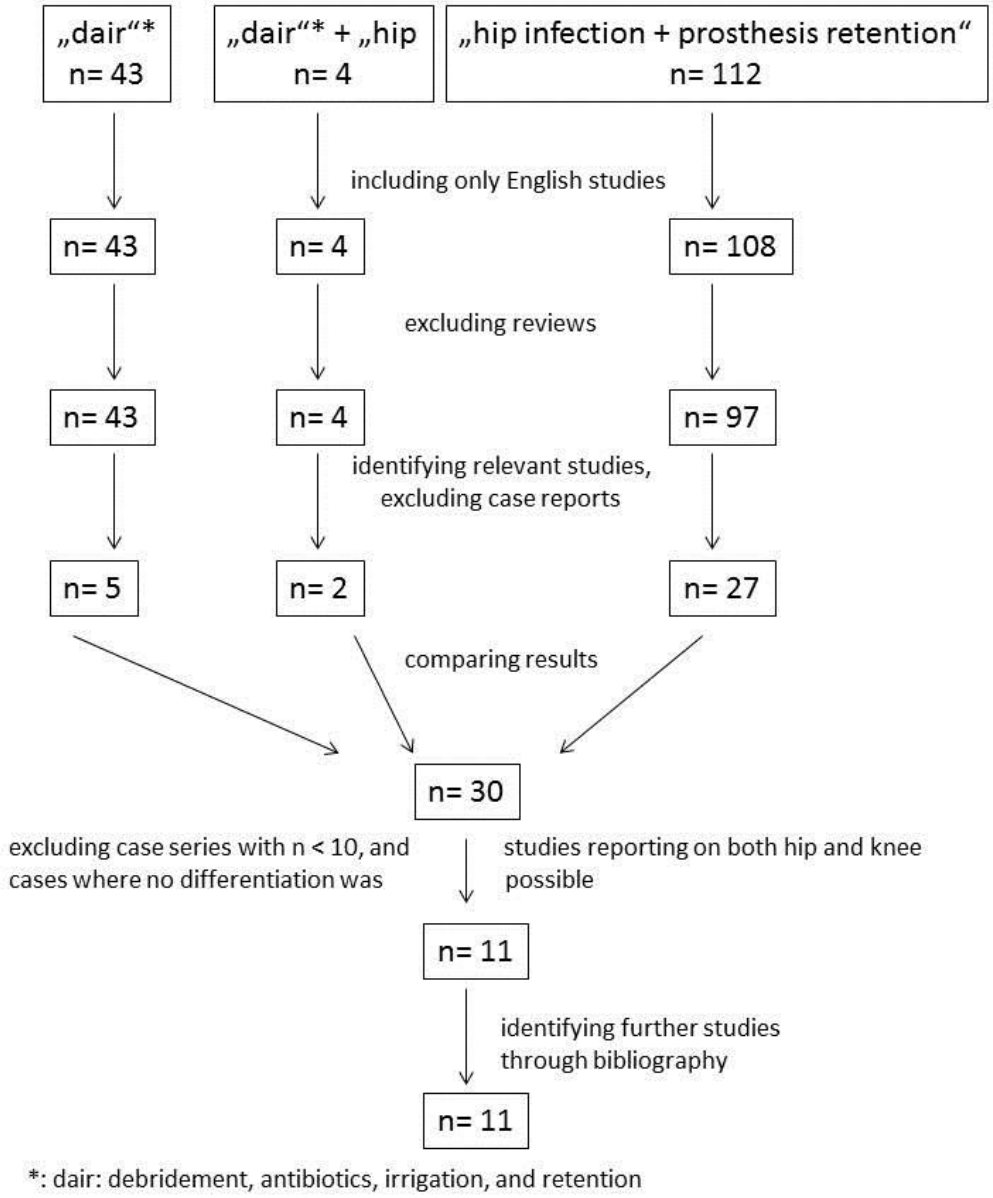
Table 3: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to the systemic antibiotic therapy.

Study	Systemic antibiotic therapy
Aboltins et al. [6]	all intravenous glycopeptide or beta-lactam for median 10 [3-29] days all oral rifampicin+fusidic acid for median 17 [6-33] months
Aboltins et al. [7]	all intravenous glycopeptide + beta-lactam for median 15 [12-34] days all oral rifampicin + fucidic acid or ciprofloxacin for median 356 [230-395] days
Anagnostakos et al. [8]	all intravenous for 4 weeks + oral for 2 weeks
Choi et al. [9]	all intravenous for 6 weeks
Crockarell et al. [10]	41/42 intravenous for 29 [2-72] days 26/42 oral after i.v. for 70 [5-376] days; 3/42 chronic suppression
Kelm et al. [11]	intravenous for 2 weeks followed by oral for 2 weeks
Kluche et al. [12]	intravenous for 6 weeks followed by oral for 6 weeks
Lee et al. [13]	intravenous for 4-6 weeks
Tsukayama et al. [2]	early: intravenous for 4 weeks; acute hematogenous: intravenous for 6 weeks

Waagsbo et al. [3]	overall duration of antibiotic therapy 0.1 [8.2-14.2] weeks, of which intravenous 4.4 [4.2-6.1] weeks
Westberg et al. [14]	overall duration of antibiotic therapy 7 [3-39] weeks

Figures

Fig. 1: Flow chart diagram showing the single steps of literature search for identification of relevant studies



*: dair: debridement, antibiotics, irrigation, and retention

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Fig. 2: Overview of treatment procedures for management of periprosthetic hip joint infections

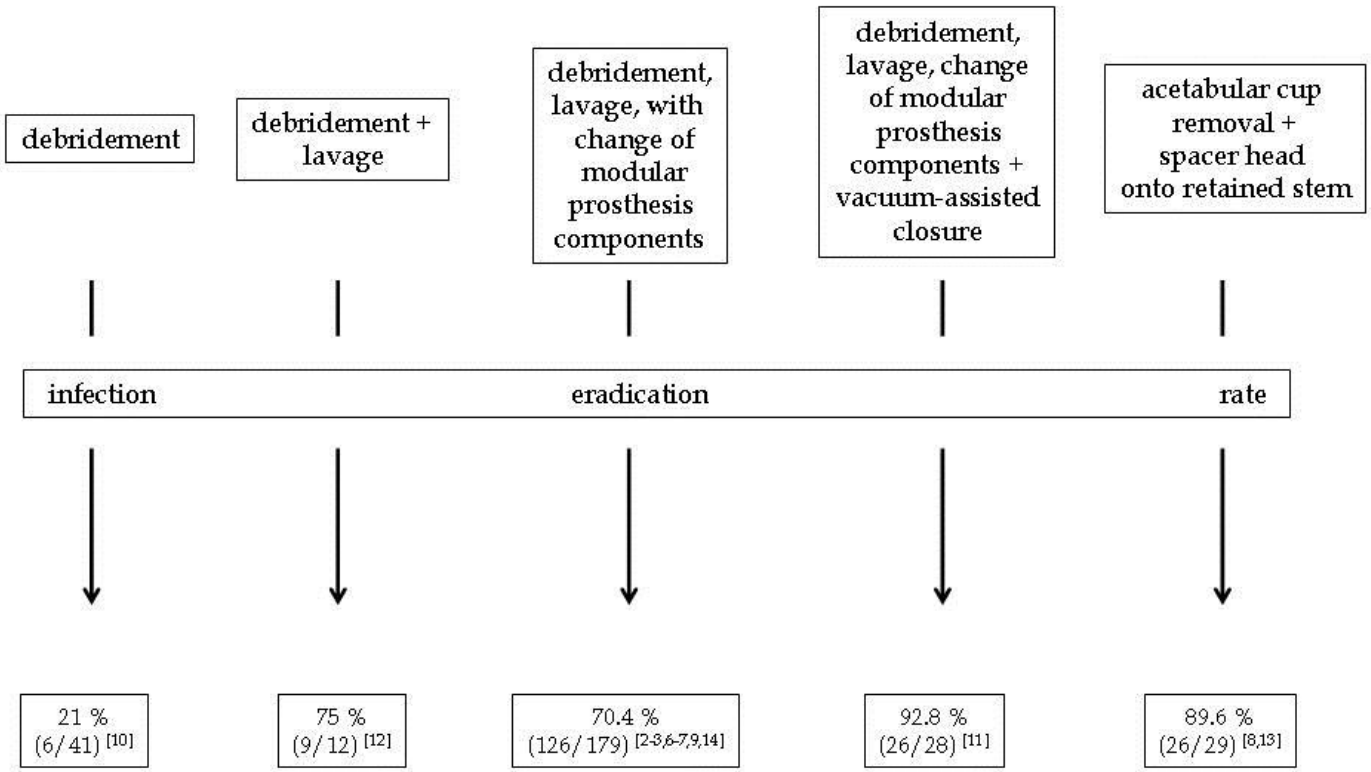

Figure Legends

Figure 1: Flow chart diagram showing the single steps of literature search for identification of relevant studies.

Figure 2: Overview of treatment procedures for management of periprosthetic hip joint infections.

Table 1: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to publication year, number of patients treated, type of infection, and level of evidence.

Table 2: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to surgical treatment modalities, -complications, infection eradication rate, and length of follow-up.

Table 3: Overview of 11 studies reporting about prosthesis retention at the site of periprosthetic hip joint infections with regard to the systemic antibiotic therapy.

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ESPS Peer-review Report
Name of Journal: World Journal of Orthopedics
ESPS Manuscript NO: 7660
Title: Can periprosthetic hip joint infections be successfully managed by debridement and prosthesis retention? A systematic literature review
Reviewer code: 00740820
Science editor: Wen, Ling-Ling
Date sent for review: 2013-11-28 11:32
Date reviewed: 2014-02-11 18:27

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS
The article is well written. The analysis of the literature well-conducted , precise, but limited. The materials and methods are adequate in a retrospective study . The analysis of the data obtained is acceptable. I would have preferred that the authors enfatizzassero their personal results as opposed to those in the literature , instead of inserting them into the analytic discourse generally. The literature reviewed is definitely part since it is only 11 studies with a total of 292 cases. And only 52 cases of late infections are quite a few . In addition, the treatment procedures are certainly very different from each other , so it is difficult to draw more conclusions precise and safe to drive in a unique treatment of infection in hip replacements . Moreover, even the authors write: " Although single studies Demonstrated high success rate exceeding 90% , the relative small number of patients treated as well as the low level of evidence does not allow for generalization of Conclusions . " . The authors also write : "Due to the relative small power of the included cases and inhomogenities in the treatment procedures and collectives Themselves it can not be stated Which antibiotic treatment is the optimal" and also " The current literature does not allow for generalization of conclusion with regard to the best treatment modality . " . But then comes to the conclusion that the work done by the authors has been absolutely useless if you can not give definite indications for treatment in case of infection of the hip , on the basis of the literature. In light of all these considerations , I therefore consider that the article can be published with modifications. That is expanding and looking for articles literature considered homogeneous . In addition , the authors should better highlight their type of treatment performed and their personal results.