Review

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Posted Date: 1 October 2024

doi: 10.20944/preprints202407.0880.v2

Keywords: Hip; Infection; Prosthesis: PJI; One-stage; Single-stage; Revision; Review; Local antibiotics; Antibacterial coatings

Review

What Is the Role of Local Antimicrobial Protection for One-Stage Revision for Peri-Prosthetic Hip Infection?

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Abstract: Antibiotic-loaded bone cement has been traditionally advocated as a key step for the success of one-stage hip revision surgery, while cementless techniques have been recently proposed with and without the use of local antibacterials as an equally successful alternative. Aim of this review is to investigate the effective role of local antimicrobial protection for one-stage cemented and cementless hip revision surgery. Twelve studies reporting the results of cemented single-stage procedure at a minimum two years follow-up were reviewed. When pooling together the data, no infection recurrence was observed on average in 83.3% of the patients (range 75.0% to 100%). Only two papers, both from the same French group, included patients treated without the use of antibiotic-loaded bone cement, with an average infection control of 95.9% in a total of 195 patients. This figure appears better that the 80.7% infection control obtained by pooling together all the remaining studies. Concerning cementless one-stage revision, a total of 17 studies, reporting on 521 patients, showed an average 90.0% (range 56.8% to 100%) no infection recurrence, at a minimum two years follow-up. Eight papers reported the outcomes of cementless implants without any local antibacterial protection and nine more described four different techniques for local antimicrobial implant protection. No comparative study investigated cementless revision with or without local antibacterial protection. Pooled data showed an average infection control of 86.7%, without the application of local antibacterials, compared to 90.1% to 100% with local antimicrobial protection, depending on the technology used. However, due to the relatively low number of patients treated with each local antimicrobial protection, no statistical difference could be found, either considering local antibacterial strategies alone or pooled together. No side effect had been reported by any local antibacterial technique. This review points out that local antibacterial protection for one-stage hip revision surgery, although safe and largely performed in the clinical setting, appears still to rely mainly on experts' opinion and on observational series with no prospective or comparative trial, hence no definitive conclusion can be drawn concerning its effective role in one-stage hip revision surgery.

Keywords: hip; infection; prosthesis: PJI; one-stage; single-stage; revision; review; local antibiotics; antibacterial coatings

1. Introduction

"Rates of peri-prosthetic joint infection (PJI) in primary total hip and total knee arthroplasty range between 0.3% and 1.9%, and up to 10% in revision cases. Significant morbidity is associated with this devastating complication, the economic burden on our healthcare system is considerable, and the personal cost to the affected patient is immeasurable" [1].

The occurrence of peri-prosthetic joint infection (PJI) generally requires the removal of the infected implant and its exchange in a single- or two-stage surgical procedure. The operative approach is determined by a combination of surgeon's experience, clinical and radiological presentations, available bone-stock and infection factors, with the majority of surgeons opting for a two-stage procedure, which has been traditionally felt as more secure and succcessful [2,3]. On the other hand, a one-stage approach does offer self-evident advantages over a staged procedure, including reduced hospitalization, costs and time to recovery [4]. Moreover, several recent studies and systematic reviews, have pointed out the lack of a statistically significant difference in infection recurrence rate after one-stage or two-stage hip revision surgery [5,6]. These observations are progressively prompting more and more surgeons to propose one-stage strategies to their patients and novel one-stage techniques have been proposed in recent years.

In fact, the first and the most often reported one-stage technique requires the fixation of the new implant with antibiotic-loaded bone cement, which is considered a key step for the success of the procedure [7]. On the other hand, more recently, various authors reported that cementless revision hip prosthesis, with or without the application of local antibiotic delivery systems, can be equally effective [6].

Aim of the present review of the current literature is to investigate the effective role of local antibacterial protection technologies for one-stage cemented or cementless hip revision surgery, to test the hypothesis that local antibiotic implant protection may have a positive impact on reducing the infection recurrence rate after this surgery.

2. The role of local antibacterial protection in cemented one-stage hip revision surgery

In the early 1970s, Dr. Hans Wilhelm Buchholz conducted extensive research on antibiotics and polymethylmethacrylate (PMMA) in the context of hip and knee replacement surgery. He consistently reported lower infection rates with the addition of gentamycin antibiotics to the bone cement. Dr. Buchholz was among the first to demonstrate the successful use of antibiotic-loaded bone cement for preventing infections in endoprostheses, as well as using single exchange arthroplasty for treating infected prostheses [8]. One-stage exchange arthroplasty, using techniques and principles similar to those originally described by Buchholz's team at the ENDO Klinik in Hamburg, Germany, has been since then adopted by various centers around the world [9–12].

The three key principles of the ENDO Klinik have been well described and recently reconfirmed [13,14]. First, the organism must be identified along with its sensitivities and minimum inhibitory concentrations. According to its original description, single-stage revision should not be performed without this information, as antibiotic treatment cannot be appropriately tailored to combat the infection. Joint aspiration is hence performed with the patient off antibiotics for at least 14 days, using an "as sterile as possible" technique, and with a culture incubation period of 14 days. The second principle is debridement. Aggressive debridement and complete removal of all infected tissues and implanted biomaterials is considered a pivotal step for the success of the technique. The third principle involves both local and systemic antibiotic delivery tailored to the identified pathogenic organism. Local antibiotic delivery is achieved through cement [15]. According to the authors that first described this method, PMMA ensures much higher tissue concentrations at the infection site than systemic administration. Bactericidal antibiotics, such as aminoglycosides, cephalosporins, fluoroquinolones, metronidazole, penicillin, and vancomycin can be advantageously mixed, while some authors consider also clindamycin an acceptable bacteriostatic option [5]. Up to 10% of the dry crystalline weight of antibiotics can be added to the cement without significant mechanical loss.

Concerning safety, while local antibiotics achieve high intra-articular concentrations with lower systemic risks, there are rare case reports of systemic complications like renal or hepatic failure, and

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allergic reactions [16]. However, pharmacokinetic studies investigating antibiotic concentrations released from PMMA showed serum and urine concentrations below toxic thresholds [17–20], while local cytotoxicity of eluted antibiotics demonstrated good cell survival/recovery capacities after high antibiotic concentration exposure for antibiotics as cephazolin, vancomycin and aminoglycosides [21,22], even if high local levels of gentamicin have been shown by some author to have a detrimental impact on osteogenesis [23]. Another big concern about prolonged local antibiotic delivery from bone cement is the development of microbial resistance. This has been disproven by several authors [24–27]. Overall, the potential toxic effects and risks of local release of antibiotics by bone cement are considered extremely low and rare and do not prevent the current widespread use of antibiotic-loaded bone cement in various clinical settings [28–30]. On the other hand, it should be emphasized that the presence of antibiotic in bone cement has been found able to reduce bacterial biofilm formation, but it may not completely inhibit its presence [31].

The scientific background of the clinical use of local antibiotics released from bone cement relies on *in vitro* [32,33] and *in vivo* studies [34,35]. Moreover, comparative clinical trials, investigating low- or high dose local antibiotics delivery and/or single versus dual antibiotics, do bring evidence that higher dose or combination of antibiotics improve post-surgical infection control compared to lower dose or single antibiotic. Jenny and co-workers, reported on a prospective, single center clinical trial, showing a statistically significant 50% reduction of infection recurrence rate after one-stage hip or knee revision surgery, using high dose gentamycin and clindamycin loaded bone cement, compared to low-dose [36]. Similarly, Smynski et al., recently reported the data from the German register, showing better infection prevention after hip prosthesis for femoral neck fracture management by using dual antibiotics in bone cement, compared to single antibiotic [37]. This study is in line and confirms a previous observation conducted in the United Kingdom [38]. However, to the best of our knowledge, there is a lack of prospective studies or systematic reviews and meta-analysis comparing local antibiotic delivery from PMMA to plain cement for one-stage treatment of peri-prosthetic hip infection.

We performed a thorough and comprehensive literature search of studies fully written or with an abstract in English on cemented and uncemented one-stage hip revision surgery for delayed periprosthetic hip infection, by searching the following internet databases,: EMBASE; PubMed/Medline; Medline Daily Update; Medline In-Process and other non-indexed citations; Google Scholar; SCOPUS; CINAHL; Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews; NHS Health Technology Assessment; http://www.google.com, with the following keywords either alone or in a variety of combinations: hip; infection; arthroplasty; prosthesis; total hip replacement; THR; THA; prosthetic hip infection; periprosthetic hip infection; exchange arthroplasty; one-stage; single-stage; cemented; cementless; uncemented. The results of all studies of 5 or more cases and a minimum follow-up of 24 months are reported in Tables 1 and 2.

Mean and standard deviations (SD) were calculated on pooled data and compared. Statistical analysis was performed using *t*-tests and Fisher's Exact test where appropriate. A p-value of <0.05 was deemed to be statistically significant.

Pooling together the data of 12 studies available for our analysis, reporting on delayed (> 6 weeks from surgery) PJI, the average success rate of one-stage antibiotic-loaded cemented hip revision is 83.2% (range 75% to 100%) (cf. Table 1).

Table 1. Data from studies reporting cemented one-stage hip revision surgery for delayed (> 6 weeks after surgery) peri-prosthetic hip infection, at a minimum follow-up of 24 months.

Author	**Year**	**Number of patients**	**Number of patients free from infection at follow-up**	**Percent of patients free from infection at follow-up**	**Follow-up (months)**			**Selection bias**	**Local antimicrobial protection**
					Min	Max	Mean		

Buchholz [39]	1981	582	448	76.8	24	132		No	Yes
Miley [40]	1982	46	40	87	32		48.5	Yes	Yes
Wroblewski [41]	1986	102	93	91.2	38.8			No	Yes
Sanzen [42]	1988	102	77	75.5	24	108		No	Yes
Raut [43]	1995	57	49	86.0	24	151	88	No	Yes
Mulcahy [44]	1996	15	15	100	24			Yes	Yes
Ure [45]	1998	20	20	100	42	205.2	118.8	Yes	Yes
Callaghan [46]	1999	12	10	83.3	120			Yes	Yes
Oussedik [47]	2010	11	11	100	66	105.7	81.6	Yes	Yes
Klouche [48]	2012	38	38	100	24	61	35	No	**No**
Zeller [49]	2014	157	149	94.9	28.1	66.9	41.6	Yes	**No**
Jenny [50]	2014	65	55	84.6	36	72		Yes	Yes
Total		1208	1005		-	-	-		
Minimum		11	-	75	24.0	61.0	35.0		
Maximum		583	-	100.0	120.0	205.2	118.8		
Mean		39.5	-	**83.2**	40.2	109.5	66.6		
SD*		38.8	-	-	27.9	46.9	30.4		

*SD: Standard deviation.

Local antibiotic(s) administration through bone cement appears as the preferred choice of the majority of authors reporting one-stage hip revision surgery. Seven our of the 12 studies included in our analysis disclosed a selection bias, as patients with draining fistula, unknown or multi-resistant pathogen(s) or immunocompromised hosts were excluded (cf. Table 1).

We found only 3 clinical trials, reporting cemented one-stage revision surgery without the use of local antibiotics. All those studies have been performed in France. Klouche and co-workers were the first to publish a striking 100% infection eradication rate at two years minimum follow-up, in a series of 38 patients [48]. In line with this, few years later, Zeller et al., in a large multi-center cohort

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study on 157 patients treated with one-stage exchange arthroplasty and twelve weeks of systemic antibiotics and no antibiotics in the cement, showed only two relapses and six new infections, with a cumulative infection control rate of nearly 95% at five years postoperatively [49]. In a more recent study, conducted in the same center [51], an overall infection eradication rate of 95.3% at a minimum two years follow-up was reported in a series of 66 patients treated either with cemented (N=21) or cementless revision prostheses (N=45), without the addition of local antibacterials. Moreover, all of these patients had a fistula at the time of surgery, actively draining in 76% of cases, a condition which is considered by many as a bad prognostic factor and even a contraindication to a one-stage procedure [52] (this study is not included in Table 1, as it does not distinguish between hip and knees).

When pooling together the data of the French studies from Klouche and Zeller (N=195) and comparing them with the results reported by all other authors (N=1013), the difference in average infection control, 95.9% versus 80.7%, is unexpectedly extremely statistically significant, in favor of no local antibiotic administration ($p<0.0001$). Similar results are obtained even excluding the oldest papers, published before year 1995. In this case, no infection recurrence is observed in 88.9% of 180 patients, a value which is still statistically inferior to the that of Klouche and Zeller ($p=0.01$).

While this comparison has obvious methodological limits, as it considers different patients' populations across various centers, with possible bias and heterogeneous material, it adds to the fact that, on the basis of the available literature, there is no clinical evidence that delivering local antimicrobials through PMMA is necessary in single-stage hip revision surgery. Hence, more than four decades after its first description, the use of antibiotic-loaded bone cement appears to remain largely based on experts' opinion and on data obtained in pre-clinical studies or comparative clinical trials in other settings [53].

3. The role of local antibacterial protection in cementless one-stage hip revision surgery

For various reasons, cementless fixation of hip implants is currently the predominant choice of surgeons, according to the UK National Joint Register [https://reports.njrcentre.org.uk/AR-Executive-Summary] and to the Swedish register [54], even if it has not been proven superior to cement in a recent systematic review [55].

Cementless one-stage revision to treat peri-prosthetic hip infection is also gaining more and more acceptance worldwide in recent years. In fact, the largest series on cemented one-stage hip revision surgery date back from four to one decade ago, while in the last 20 years a growing number of papers reporting on cementless one-stage reimplantation can be found (cf**. Table 2**).

Seventeen observational studies reporting on delayed peri-prosthetic hip infection, treated with cementless one-stage revision, for a total of 521 patients were retrieved by our search. No randomized, prospective controlled trial, comparing different cementless one-stage techniques could be found. The majority of papers described retrospective series, without a control group (Level of evidence: IV). The number of cases ranged from 5 to 111 (mean 30.6, ± 25.0). Overall, at an average follow-up of 65.5 ± 22.5 months (range 24 to 78 months), infection control was obtained in 90.0% of the cases (range 56.8% - 100%)(Table 2).

Table 2. Data from studies reporting cementless one-stage hip revision surgery for delayed (> 6 weeks after surgery) peri-prosthetic hip infection, at a minimum follow-up of 24 months.

Author	Year	Number of patients	Number of patients free from infection at follow-up	Percent of patients free from infection at follow-up	Follow-up (months)			Selection bias	Local antimicrobial protection
					Min	Max	Mean		

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Garcia [56]	2004	7	7	100	24			No	No
Rudelli [57]	2008	32	30	93.8	63	183	103	Not reported	No
Winkler [58]	2008	37	34	91.9	24	96	52.8	Yes	Antibiotic-loaded allografts
Yoo [59]	2009	12	10	83.3	39.6	135.6	86.4	Yes	No
Wolf [60]	2014	37	21	56.8	24			No	No
Bori [61]	2014	24	23	95.8	25	94	45	Yes	No
Li [62]	2015	6	6	100.0	78	187.2	103.2	Yes	No
Born [63]	2016	28	28	100.0	24	180	84	Yes	No
Ebied [64]	2016	33	32	97.0	48	96	60	Yes	Antibiotic-loaded allografts
Whiteside [65]	2017	21	20	95.2	25	157	63	No	Intra-articular antibiotic infusion
Lange [66]	2018	56	51	91.1	24		48	No	Gentamicin collagen fleece
Capuano [67]	2018	5	5	100.0	24	36	29.3	No	Antibiotic-loaded hydrogel coating
Ji [68]	2019	111	99	89.2	24	107	58	No	Vancomicin or Imipenem powder and intra-articular antibiotic infusion

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Pellegrini [69]	2021	10	10	100.0	24	60	37.2	Yes	Antibiotic-loaded hydrogel coating
Ji [70]	2022	29	26	89.7	24	133	85	No	Intra-articular antibiotic infusion
Dersch [71]	2022	38	35	92.1	24	187.2	67.2	Yes	Antibiotic-loaded allografts
Mangin [72]	2023	35	32	91.4	24	132	60	Yes	No
Total		521	469		-	-	-		
Minimum		5	-	56.8	24.0	36.0	29.3		
Maximum		111	-	100.0	78	187.2	103.2		
Mean		30.6	-	**90.0**	31.9	127.4	65.5		
SD*		25.0	-	-	16.2	48.4	22.5		

*SD: Standard deviation.

Eight studies reported one-stage cementless revision without the use of local antibiotics. Among these, 5 reported a selection bias, excluding patients with open fistulas and/or severe bone loss and/or unknown or multi-resistant pathogen(s) or immunocompromised hosts. Moreover, Bori et al. [61] and Born et al. [63] did report the use of antibiotic-loaded cemented cups in some cases, while Yoo et al. [59] performed only cup revision in 4 patients out of the 12 treated. Pooling the results of all studies reporting no local antibiotic administration together (N=181), an average infection control of 86.7% (range 56.8% - 100%), at a mean follow-up of 80.3 ± 23.4 months, can be calculated (cf. Table 3).

The remaining nine studies reported the results on four different local antibiotic delivery techniques, which, on the average, provided the following no infection recurrence rates: intra-articular post-operative antibiotic infusion or local antibiotic vancomicin powder application at the time of surgery: 90.1%; antibiotic-loaded collagen-fleece: 91.1%; antibiotic-impregnated allografts: 93.5%; antibiotic-loaded hydrogel coating: 100% (cf. Table 3).Three studies excluded patients with open fistulas, unknown or multi-resistant pathogen(s) or immunocompromised hosts (cf. Table 2). No side effects were reported with the use of any local antibacterial technology. Due to the relative low number of patients, no statistical difference could be demonstrated ($p > 0.05$) by single or pooled together local antimicrobial protection systems, compared to no local antibiotic application.

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Table 3. Local antibacterial protection and infection recurrence for one-stage cementless hip revision: pooled results.

Local antibacterial protection	Number of patients	Number of patients free from infection at follow-up	Percent of patients free from infection at follow-up (mean, min, max)	Follow-up (months) (mean and SD*)
None [56,57,59–63,72]	181	157	**86.7** (56.8-100)	80.3 ± 23.4
Intra-articular antibiotic infusion or local antibiotic vancomicin powder [65,68,70]	161	145	**90.1** (89.2-95.2)	68.7 ± 14.4
Gentamicin-loaded collagen fleece [66]	56	51	**91.1**	48
Antibiotic-loaded allografts [58,64,71]	108	101	**93.5** (91.9-92.1)	60.0 ± 7.2
Antibiotic-loaded hydrogel coating [67,69]	15	15	**100.0**	30.1 ± 6.8

*SD: Standard deviation.

One study [73] reported the results of single-stage cementless revision surgery without local antibiotic delivery for the treatment of early infections (< 6 weeks after implant); this report showed a remarkably low infection control (56% or 15/27 patients), at a mean follow-up of 50 months (range, 27-89 months). This observation compares to a similar one, conducted by Riemer and co-workers, that, with the use of gentamicin-loaded collagen fleece, reported successful implant retention at mean follow-up of 60 months in 18/18 patients [74].

3. Discussion

In this review we addressed the relative role of antibacterial local protection in one-stage cemented or cementless revision surgery for peri-prosthetic hip infection.

While this analysis does confirm previous observations concerning cementless one-stage hip revision success rates similar or even superior to that of cemented implants [6,75,76], the reviewed data do not support conclusively the need of local antibiotic delivery for periprosthetic infection control.

In particular, our findings challenge the superiority of antibiotic-loaded cemented one-stage hip revision surgery and contradicts the traditional prescription of antibiotic-loaded bone cement as a key factor to perform a successful one-stage hip revision surgery [8,77]. In the lack of comparative trials, this is mainly due to the French experience, reported by Klouche, Zeller and co-workers [10,48,49]. Further analysing those, data in light of the current knowledge regarding biofilms and bacterial adhesion capabilities, it appears evident the limit of bone cement as a local antibacterial implant protection system. In fact, antibiotic-loaded bone cement is only applied to the interface between the cup and/or the stem of the prosthesis, leaving all the extramedullary and the modular

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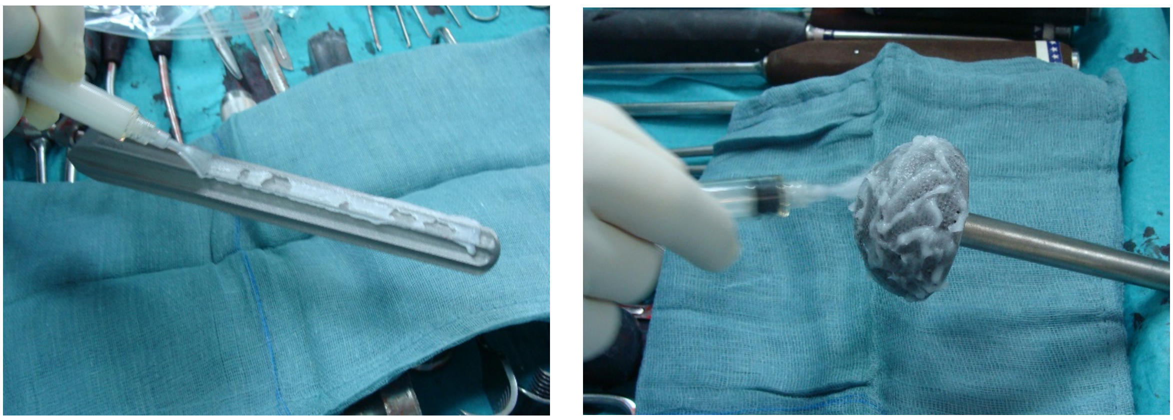
parts of the implant unprotected. This technical limit may not be overcome unless antibiotic-loaded bone cement is used in combination with other technologies able to protect also the uncemented parts of the prosthesis. Moreover, not all the antibiotic-loaded bone cements are the same and do provide the same antibiotic elution. Manual mixing of antibiotics to PMMA has been shown to provide significantly different release of various antibacterial, compared to pre-manufacture antibiotic-loaded bone cement [78]. Single or combinations of antibiotics, their relative concentration in bone cement and the porosity of PMMA are some of the many factors that come into play and determine the effective pharmacokinetic of the local antibiotic administration [79,80]. Finally, biofilms and small colony variants of bacteria have been retrieved in antibiotic-loaded bone cement [81,82], witnessing the ability of bacteria to overcome even local antibiotic protection, if favourable conditions to their persistence are met. The lack of a standard for local antibiotic administration though bone cement may well explain, among other factors, the wide range of results reported in the literature.

On the other side, our review reveals that also one-stage cementless hip revision surgery with local antibacterial protection has not been proven more effective that without in comparative clinical trials; moreover, when pooling together the results of single or combined local antibacterial protection strategies, no statistically significant difference in infection control can be demonstrated, compared to one-stage cementless hip revision without the use of local antibacterials. However, our results concerning the efficacy of local antibacterial protection in this setting should be interpreted with caution, due to many limitations of the material available for our analysis. First of all, the number of patients treated with each local antibacterial modality is quite low and heterogeneous, thus reducing the validity of the comparison of results. Additionally, pooling together the results of the patients treated with different local antimicrobial strategies can be questionable, as those chosen by the different authors were completely different one from the other, both as to concern the type of treatment and the site of application. As an example, while the antibiotic-loaded hydrogel coating may be applied to all the implant surfaces and components (cf. Figure 1), vancomycin powder, local antibiotic irrigation and other technologies may not. This may have a strong impact on the final outcome, as it is well known that the primary step of bacteria colonizing an implant is to attach to the inert surfaces of the biomaterials and immediately start forming the biofilms [83].



(**a**) (**b**)

Figure 1. Application of the DAC antibiotic-loaded hydrogel coating to (**a**) a cementless hip stem revision prosthesis and (**b**) to an acetabular cup.

If the implant surface is effectively protected by an antibacterial coating, *several in vivo* and clinical studies have shown to be extremely effective in preventing implant-related infection development [84–86]. Moreover, while most of the proposed solutions to provide local antimicrobial protection did act at the very time of surgery, others, like local antibiotic irrigation, may only take effect after surgery, when the bacteria eventually present in the surgical field had the time to attach to the implant and hence become difficult to be reached by intra-wound irrigation.

 doi:10.20944/preprints202407.0880.v2

Moreover, it is worth noting that 5 out of 8 studies, reporting on one-stage treatment without local antibacterials, have been performed on selected patients with less severe infection, minor bone involvement and better hosts. In the only direct comparison between a single- and two-stage exchange, Wolf et al. [60] showed a mean infection control exceeding 96% after two-stage, compared to less than 57% after cementless single-stage without the use of local antibiotic protection. Further analysing the data, the authors provide evidence that the difference between the two treatments was due to the better results obtained with a two-stage approach in more compromised hosts, while one-stage and two-stage did perform equally well, when normal hosts and early infections were involved. Selection bias is also a well know limit when comparing the results of one-stage procedure with two-stage, as many authors prefer a staged approach to manage the most complicated cases and inevitably most of the retrospective series reported on one-stage include less severe patients' populations [87].

Another limitation of the present review is that it did not explore how patient factors such as co-existing conditions, age, body mass index, gender, type of implant, prior surgeries, etc., might influence the outcomes. It also did not assess different surgical approaches including the type of hip revision prosthesis, the surgical technique, or the need for bone grafts. The role of the pathogen(s) and their antibiotic resistance profile was also not investigated, as that of systemic antibiotic administration and the use of single or dual local antibiotics. Furthermore, our analysis did not distinguish between cases of infection recurrence due to the same or to a different pathogen. Finally, comparison of historical studies with the most recent ones can be biased, as across the years the diagnostics and even the definition itself of peri-prosthetic joint infection has evolved and changed several times.

Its main limitations notwithstanding, this review shows that single-stage exchange arthroplasty is a viable option for the treatment of chronic periprosthetic hip infections. Local antibacterial treatment is safe, even if its superiority over no local antimicrobial protection is not proven. The fact that, with the current data available, is not possible to prove the clinical benefit of local antibacterial protection for one-stage hip revision surgery for the treatment of peri-prosthetic infection has a clear impact on research, clinical and medico-legal aspects. This also may ground the ethical basis for designing prospective comparative studies with and without local antibacterial protection. In fact, the limitations and biases in current literature underscore the need for large-scale, multicentre, prospective, randomized trials to definitively determine the real impact of local antibacterial implant protection, if any. Even if logistical challenges such as the low incidence of the disease, small patient populations, long-term follow-up requirements, and variations in microorganisms make conducting such studies exceptionally difficult, such studies are possible and have been performed successfully in other clinical settings [88,89].

Author Contributions: Conceptualization, C.R.; methodology, C.R., H.D.S., M.T.; formal analysis, L.B., G.B.; investigation, C.R., L.B., G.B.; writing—original draft preparation, C.R.; writing—review and editing, C.R., H.D.S., M.T.. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: CR is co-inventor and receives royalties from Novagenit Srl, the company producing the DAC antibacterial hydrogel coating. The remaining authors declare that they have no competing interests.

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