

1 **Do Cultures Obtained During Primary THA Predict the Likelihood of Revision?**

Running Title: Hip Arthroplasty with Positive Cultures

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Comentado [PM1]: AU: Avoid the term “predict.” First, there is no “predicting” in a retrospective study. Predicting involves looking ahead, and this study looked back. Second, “predict” involves a lot more causality than you established.

I think your question is a good title: “Are unexpectedly positive culture results obtained during elective THA associated with an increased likelihood of revision?” Suggest you use that. ED

Author response: Thank you for your suggestion. The proposed title sounds good for us.

2 Abstract

3 *Background* There can be unexpectedly positive culture results during elective hip arthroplasty,
4 but the degree to which these are associated with an increased risk of subsequent premature
5 revision is not known.

6 *Question/purpose* Are unexpectedly positive culture results obtained during elective THA
7 associated with an increased likelihood of revision within 5 years of the procedure?

8 *Methods* Between March 2007 and March 2011, the hip unit at our institution performed elective

9 primary THA in 829 patients. We systematically collected three samples in ~~521.6%~~ (428 of 829)

10 of the interventions. Of those, 26 patients were excluded because of sampling errors; ~~943.9%~~

11 (402 of 428) had samples that were collected systematically were eligible for the study. We only

12 considered one hip randomly in bilateral procedures (~~43.5%~~, 15 of 428); patients presenting with

13 acute (< 3 months) periprosthetic joint infection undergoing open debridement (~~4.0%~~, 16 of 402)

14 and patients who died before 5 years of follow-up (~~21.7%~~, seven of 402) were excluded from the

15 study, leaving ~~90.5%~~ (364 of 402) eligible for analysis in this retrospective study of a previous

16 prospective trial. No patient included in the final analysis was lost to follow-up within 5 years

17 from the index surgery. The patient group consisted of ~~521.6%~~ (188 of 364) women with a mean

18 \pm SD age of 64.8 ± 13.9 years.

19 *Results* Positives culture results were associated with a higher risk of revision within 5 years of

20 the index surgery. The proportion of revision surgery was higher in the group with positive

21 culture results than in those with negative results [(~~110.8%~~ [eight of 77] versus ~~2.4%~~ [seven of

22 290]; $p = 0.01$). The difference was mainly attributable to a higher proportion of aseptic

23 loosening in those with positive culture results than in those with negative results (~~8.1%~~ [six of

24 74] versus ~~1.4%~~ [four of 290]; $p = 0.01$). After a multivariable analysis, the only independent

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Response: Ok

25 variable associated with 5-year revision surgery was the presence of positive results during THA
26 (odds ratio 4.9; 95% confidence interval, 1.72 to 13.99).

27 *Conclusion* Our findings suggest that bacterial contamination during THA is associated with an
28 increased likelihood of early revision. This higher risk of revision is mainly because of presumed
29 aseptic loosening; thus, efforts should focus on the need to rule out infection. These results not
30 only open new questions that should be answered in new prospective and well-designed studies,
31 but also may help to better select patients to obtain a better outcome after THA.

32 *Level of Evidence* Level III, therapeutic study.

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33 **Introduction**

34 The main causes of prosthetic revision are aseptic loosening, mechanical failure, and prosthetic
35 joint infection (PJI) [12, 14]. Despite efforts to optimize patients to prevent PJI, the infection
36 burden across several international registries has increased in recent years [15]. To reduce the
37 incidence of revision surgery, it is necessary to elucidate the physiopathology of these
38 complications. Intraoperative contamination from skin microbiota or the environment occurs
39 frequently, even when all procedures to reduce contamination are adequately implemented [3].
40 We reported a prospective observational study in which no relationship between intraoperative
41 cultures during primary THA and the risk of postoperative acute PJI was found [6]. In addition,
42 the relationship between bacterial contamination and the risk of surgical site infection was
43 documented in a large study including nonorthopaedic surgeries [7] and one including THA [9].
44 These studies showed a correlation among positive culture results, prolonged wound leakage,
45 and PJI. However, the later study [9] followed patients for only 2 years and the authors focused
46 on documented PJI. It has been suggested that some presumed aseptic loosening revisions are
47 actually undiagnosed, missed, low-grade infections, especially in patients presenting with early
48 loosening [5].
49 More recently, several studies have questioned whether what is commonly diagnosed as aseptic
50 loosening is, in fact, aseptic, or whether it always or nearly always undiagnosed PJI. When a
51 revision is performed within the first 2 years from primary implantation, the etiology of failure is
52 more likely to be a prosthetic joint than aseptic loosening [12]. Additionally, there is a
53 correlation between positive intraoperative culture results and the age of the primary
54 prosthesis time from index arthroplasty to revision, supporting that early loosening is more often
55 caused by missed low-grade infections than late loosening [13]. Thus, it is reasonable to suspect

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Comentado [KH3]: AU: Do you mean "the patient's age at the time of implantation of the primary prosthesis"?

Response: no, I mean "time from index arthroplasty to revision". The sentence has been clarified.

56 that much of these so-called “early aseptic loosening” are, in fact, a missed diagnosis of low-
 57 grade PJI. Recently, the physiopathology of aseptic loosening has been evaluated [11], and some
 58 studies using implant sonication have documented the presence of microorganisms in up to 12%
 59 to 33% of patients with a preoperative diagnosis of aseptic loosening [2, 5, 10, 16, 17]. Thus, it
 60 seems reasonable to evaluate the potential association between positive culture results during
 61 primary arthroplasty and the risk of revision surgery for different causes after long-term follow-
 62 up. Although we previously found no relationship between intraoperative cultures and
 63 postoperative PJI [6][REF], we aimed, in this study, to disclose whether those cultures predicted
 64 the likelihood of early revision. Therefore, we asked: Are unexpectedly positive culture results
 65 obtained during elective THA associated with an increased likelihood of revision within 5 years
 66 of the procedure?

Comentado [KH4]: AU: Can you provide a reference for this previous study?

67 **Patients and Methods**

68 *Study Design and Setting*

69 This was a single-center, retrospective, comparative study in the subspecialized hip unit of an
 70 urban tertiary hospital, including patients who underwent THA from March 2007 to March 2011.
 71 This current review is based on systematically collected samples (n = 402) during the
 72 aforementioned period in the framework of a previous pilot study evaluating the relationship of
 73 cultures performed during primary THA with postoperative acute PJI (< 3 months) [6]. We
 74 leveraged and exploited the database after a have performed an thorough reviewupdate of the
 75 database and thoroughly revised all included data. During that period, two specialized surgeons
 76 in our hip unit routinely collected three samples for culture in a standardized manner during
 77 elective THA. Patients in whom the sample collection was not standardized were not included in
 78 the study.

Comentado [KH5]: AU: I'm unsure of what you mean in this sentence. Can you revise this sentence for better clarity?

Comentado [KH6]: AU: I've edited this sentence in an effort to clarify what you mean here. All right as edited?

Original: During that period standardized collection of 3 samples for culture during elective THA was routinely performed by two specialized surgeons of the hip unit.

Response: yes, it is alright as edited. Thank you very much.

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79 *Patients*

80 Between March 2007 and March 2011, the hip unit at our institution performed elective primary
81 THA in 829 patients. Three samples were systematically collected in 51.6% (428 of 829) of the
82 interventions. Twenty-six patients were excluded because of sampling errors; thus, 93.9% (402
83 of 428) had systematic sample collection and were eligible for the study. We only considered one
84 hip randomly in bilateral procedures (3.5%, 15 of 428), whereas patients presenting with acute (<
85 3 months) PJI undergoing open debridement (4.0%, 16 of 402) and patients who died before 5
86 years of follow-up (1.7%, seven of 402) were excluded from the study, leaving 90.5% (364 of
87 402) eligible for analysis in this retrospective analysis of our previous prospective trial [6] (Fig.
88 1). As mentioned, all patients were followed for a minimum of 5 years as the considered cutoff
89 point to consider a revision as “early.”

90 *Participants' Baseline Data*

91 The patient group consisted of 51.6% (188 of 364) women with a mean \pm SD age of 64.8 ± 13.9
92 years. The main diagnosis was primary osteoarthritis in 92.3% (336 of 364) of the patients,
93 followed by avascular necrosis in 4.7% (17 of 364) and hip dysplasia in 1.9% (seven of 364). No
94 differences were found between the negative and positive culture results groups regarding patient
95 demographics (Table 1). Of the 386 patients included in the analysis, 20.3% (74 of 386) had at
96 least one positive intraoperative culture result; 18.1% (70 of 386) had one positive sample and
97 1.1% (four of 386) had two positive samples. In three patients, the cultures yielded different
98 microorganisms and in one, the same microorganism was isolated in both samples. There was no
99 patient in whom all three samples had a positive result. According to the type of sample, synovial
100 fluid samples were positive in 13.7% (50 of 364), swab samples were positive in 4.1% (15 of
101 364), and solid samples were positive in 3.6% (13 of 364).

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102

103 *Surgical Care*

104 The preoperative workup for THA included a physical examination, plain radiographs, and
105 laboratory tests. All primary THAs were performed in a standard, nonlaminar air-flow operating
106 room. All patients received the standard prophylaxis given in our hospital, which consisted of 1.5
107 g of intravenous cefuroxime during the induction of anesthesia, followed by a second dose 2
108 hours later. Patients with a beta-lactam allergy received aztreonam plus teicoplanin. All
109 procedures were performed through an anterior-lateral transgluteal approach. No antibiotic-
110 loaded cement was used whenever cemented prostheses were implanted. We excluded patients
111 who had an early (within the first 12 weeks of primary arthroplasty) acute PJI treated with
112 surgical debridement and replacement of all mobile components (femoral head and acetabular
113 liner).

114 *Cultures*

115 Samples were obtained immediately after arthrotomy, as follows: Synovial fluid was aspirated,
116 50% (approximately 1-3 ml) of the sample was inoculated into aerobic blood culture flasks, and
117 the rest was inoculated into anaerobic blood culture flasks (BACTEC 9240 system; BD
118 Diagnostic Systems). A solid sample from a capsule was taken and placed in a sterile container.
119 A swab culture was obtained by passing a sterile swab over the joint surface. The swab was
120 immediately placed in transport medium (AMIES Transport Medium). Blood culture flasks
121 containing aspirated synovial fluid were incubated in the BACTEC 9240 system for up to 5 days.
122 Culture samples with positive results were gram-stained, and microorganisms were identified
123 using conventional microbiological methods. Homogenized periprosthetic tissue and swabs were
124 cultured in thioglycolate broth, blood agar in aerobic conditions, and Schaedler agar in anaerobic

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125 conditions. All samples were incubated for up to 5 days. Positive cultures were regrown in an
126 appropriate medium. All isolated microorganisms were identified with standard biochemical
127 procedures.

128 *Variables*

129 Age, gender, BMI, American Society of Anesthesiologists score, duration of surgery in minutes,
130 results of cultures performed during primary arthroplasty, performance of revision surgery,
131 reason for revision surgery (such as aseptic loosening, infection, instability, or periprosthetic
132 fracture), and results of cultures performed during the revision procedure were gathered
133 retrospectively. At follow-up, aseptic loosening was considered present when there were pain
134 and radiologic signs of loosening without clinical symptoms or signs of infection, negative
135 cultures, and histologic findings were negative for infection according to Feldman's criteria [4].
136 We did not use the implant sonication technique for culturing in any patient.

137 *Outcomes*

138 The main endpoint was revision for any reason, defined as the need to replace at least one
139 component of the prosthesis (either the stem or cup) for any cause within 5 years of implantation
140 of the prosthesis.

141 *Ethical Approval*

142 We obtained ethical review board approval for this study.

143 *Statistical Analysis*

144 Continuous variables are reported as the mean \pm SD, and were compared using a t-test.
145 Categorical variables are reported as percentages and absolute numbers, and were compared
146 using Fisher's exact test. A two-sided p value < 0.05 was considered statistically significant. For
147 the multivariable analysis, variables with a p value < 0.2 were subjected to further selection

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148 using a forward logistic regression method. A log-rank test was used to compare the cumulative
149 probability of revision according to the results of intraoperative cultures. Analyses were
150 performed using the SPSS Statistical Package, version 20.0 (SPSS, Inc).

151 **Results**

152 *Association Between Positive Culture Results at the Time of THA and Risk of Early Revision*

153 We found that unexpectedly positive culture results obtained during elective THA were
154 associated with a higher risk of revision within 5 years of the index surgery. The rate of revision
155 surgery was higher in patients with positive culture results than in those with negative results
156 (10.8% [eight of 77] versus 2.4% [seven of 290]; $p = 0.01$). The difference was attributable to a
157 higher rate of aseptic loosening among patients with positive culture results than among those
158 with negative results (8.1% [six of 74] versus 1.4% [four of 290]; $p = 0.01$), while the difference
159 in other causes for revision was not different. The cumulative probability of revision surgery
160 (Fig. 2) was higher in patients with positive culture results than in those with negative results
161 (log-rank test: $p = 0.001$).

162 The only variable that was associated with revision surgery was having at least one positive
163 sample at the time of THA. After controlling for age and cultures taken during primary THA, the
164 only independent variable associated with 5-year revision surgery was the presence of positive
165 results during THA (odds ratio: 4.9; 95% confidence interval, 1.72 to 13.99). Of the 16 patients
166 undergoing revision surgery, eight had positive culture results at the time of the primary index
167 surgery: in five patients, the same microorganism was isolated during the revision procedure
168 (Patients 1, 2, 4, 8, and 11). In two patients, the intraoperative culture results were all negative
169 (Patients 3 and 9), and in one patient, culturing was not performed during the revision procedure
170 (Table 2).

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Ok

171 **Discussion**

172 The relationship between bacterial contamination and the risk of surgical site infection has been
173 documented [7, 9]. Some authors have suggested that presumed aseptic loosening revisions may
174 actually be undiagnosed missed low-grade infections [5]. The relationship between positive
175 cultures and the likelihood of revision remains unclear. Thus, our aim was to disclose whether
176 cultures obtained during primary THA predicted the likelihood of early revision. Our results
177 suggest that at least one positive culture result obtained during THA is associated with an
178 increased rate of revision. This higher revision rate was because of a higher rate of aseptic
179 loosening in those with a positive culture result than in those with a negative result. No other
180 variable was associated with a higher revision rate.

181 *Limitations*

182 The present study has some inherent limitations. Most importantly, because the study was
183 retrospective, certain biases may have influenced the results. Because revision surgery is often
184 performed as an elective procedure because of a symptomatic joint and not all patients are
185 systematically screened for infection at exactly 5 years, an unavoidable assessment bias might
186 have influenced our findings. However, all patients underwent surgery with the same specialized
187 surgeons of our hip unit using the same surgical procedure and the same protocols, including the
188 protocols for obtaining intraoperative samples. Unfortunately, no reliable data regarding beta-
189 lactam allergies were gathered for the whole cohort; thus, the possible influence of alternative
190 prophylactic antibiotics [1] on the results was not evaluated. Data regarding other factors related
191 to a high risk of PJI and/or early loosening were collected; for instance, the type of implant
192 design, type of fixation, smoking habits, preoperative hemoglobin A1c values, or previous
193 corticosteroid injections. Although the standardized use of sonication of the explanted

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194 components during the revision procedure may have improved the sensitivity by which we
195 detected PJI, these finding would not have modified the overall rate of revision within 5 years
196 (the only difference would have been the reason for revision).

197 *Association Between Positive Culture Results at the Time of THA and the Risk of Early Revision*

198 We found that unexpectedly positive culture results obtained during elective THA were
199 associated with a higher risk of revision within 5 years of the index surgery. Because some
200 presumed aseptic loosening revisions are actually undiagnosed missed low-grade infections [5],
201 and because these unrecognized infections have a negative impact on the outcome after revision
202 surgery [2, 10, 16], efforts should focus on the need to rule out infection.

203 Similarly, Jonsson et al. [8] obtained four swabs during surgery in 90 total joint arthroplasties
204 and evaluated the risk of PJI after a median follow-up of 13 years. The reported rate of revision
205 was twice as high in patients with positive cultures as in those with negative culture results
206 (26.8% versus 12.2%). Knobben et al. [9] obtained cultures during surgery in 100 THAs and
207 found an association between positive culture results and PJI (16.6% in the culture-positive
208 group versus 1.6% in the culture-negative group). However, they did not analyze the rate of
209 revision surgery for other causes, and the follow-up duration was 2 years.

210 These results not only open new questions that should be answered in new prospective and well-
211 designed studies, but also may help to better select patients in order to obtain a better outcome
212 after THA.

213 *Conclusion*

214 The presence of unexpectedly positive intraoperative culture results is common (20.3%) and is
215 associated with an increased risk of any-cause 5-year revision surgery (10.4%), mainly because
216 of aseptic loosening. We encourage to focus efforts on early loosening cases to rule out infection.

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217

Acknowledgments

None.

Comentado [KH8]: AU: Please list any nonfinancial acknowledgments. They should read “We thank...” Note the nature of the contribution and provide the individual’s highest academic degree.

Author response: added “none”.

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Legends

Fig. 1 This flowchart shows the patients who were included in this study. The main endpoint was the performance of early revision (< 5 years from the index surgery) for any cause. *Patients presenting with early (within the first 12 weeks of primary arthroplasty), acute PJI were treated with surgical debridement and replacement of all mobile components.

Fig. 2 This survival curve depicts the higher cumulative probability of revision surgery among patients with positive culture results.

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Table 1. Demographics of the 364 patients according to the results of cultures obtained during THA

Characteristics	Intraoperative culture results (whole cohort, n = 364)		Mean difference or odds ratio (95% confidence interval)	p value
	All negative 80.7% (290)	≥ one positive 20.3% (74)		
Age in years, mean ± SD	65.4 ± 13.4	63.2 ± 16.5	2.8 (-1.1 to 6.8)	0.16
Gender, women, % (n)	53.4 (154)	34.5 (46)	0.7 (0.4 to 1.2)	0.30
ASA score, % (n)				
I	22.4 (65)	34.3 (25)		
II	61.0 (177)	54.1 (40)		
III	15.5 (45)	11.0 (8)		
IV	1.0 (3)	0		
≥ III	16.2 (47)	11.0 (8)	0.6 (0.3 to 1.4)	0.28
BMI in kg/m ² , mean ± SD	27.8 ± 4.3	28.4 ± 4.4	-0.5 (-1.7 to 0.6)	0.34
Surgical time in minutes, mean ± SD	116.5 ± 28.6	115.0 ± 28.2	1.4 (-5.7 to 8.5)	0.42
Reason for THA, % (n)				
OA	91.4 (265)	96.9 (71)	2.2 (0.6 to 7.6)	0.23
Other than OA	8.6 (25)	4.1 (3)		
AVN	5.2 (15)	3.7 (2)		
Dysplasia	2.1 (6)	1.4 (1)		
Inflammatory disease	10.7 (2)	0		
Other	10.7 (2)	0		

Comentado [KH1]: AU: In your tables, when numbers are greater than 5 to 10, please round to the nearest whole number; eg, 80% (290).

Comentado [KH2]: AU: At the bottom on this tables, please define all abbreviations in a footnote.

Response: The abbreviations are introduced at the bottom

Comentado [KH3]: AU: In the main text, you report data for women. Perhaps you could provide the data for women instead of men here, for consistency between the text and table?

OK.

Any complication resulting in revision within 5 years, % (n)	2.4 (7)	10.8 (8)	4.9 (1.7 to 13.9) 6.3 (1.7 to 22.9)	0.01
Aseptic loosening	1.4 (4)	8.1 (6)		0.01
Chronic infection	0.3 (1)	1.4 (1)		
Instability	0.3 (1)	0		
Periprosthetic fracture	0.3 (1)	1.4 (1)		

IQR = interquartile range; ASA = American Society of Anesthesiologists; OA = osteoarthritis; AVN = avascular necrosis.

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Table 2. Characteristics of the 16 patients undergoing any-cause early revision surgery (< 5 years from the index procedure to revision)

Patient	Gender/Age	BMI in kg/m ²	Beta-lactam allergy	Indication for primary THA	Indication for early revision ^a	Number of positive culture results at the primary THA	Isolated microorganism at the primary THA	Number of positive culture results at revision	Isolated microorganism at revision	Histology at the revision ^b
1	W/63	30.0	No	OA	Chronic infection	1	CNSMR	6/6	CNSMR	30
2	M/49	27.0	No	OA	Aseptic loosening	1	CNSMS	1/5	CNSMS	0
3	W/73	27.0	Yes	OA	Aseptic loosening	1 1	CNSMS CNSMR	0/6	Negative	0
4	M/53	27.4	No	AVN	Aseptic loosening	1	CNSMS	1/6	CNSMS	0
5	W/77	25.5	No	OA	Periprosthetic fracture	0	Negative	1/5	CNSMR	0
6	W/72	29.9	No	OA	Chronic infection	0	Negative	5/6	CNSMR	25
7	W/67	32.9	No	OA	Aseptic loosening	1	CNSMR	N/A	N/A	N/A
8	W/40	29.7	No	Dysplasia	Aseptic loosening	1	CNSMS	1/6	CNSMS	0

Comentado [SSL1]: AU: The nouns that go along with "gender" are "women" and "men" not "females" and "males".

Please change the "F"'s in this column to "W". ED

Author response: ok.

As suggested, the column entitled "Months from THA to revision" has been removed.

9	W/69	287.9	No	OA	Periprosthetic fracture	1	CNSMS	0/3	Negative	N/A
10	M/38	265.7	No	OA	Metallosis	0	Negative	0/6	Negative	0
11	M/57	32.4	No	OA	Metallosis	1	CNSMR	2/6	CNSMR	0
12	M/75	210.8	No	OA	Aseptic loosening	0	Negative	0/6	Negative	0
13	M/47	265.9	No	AVN	Aseptic loosening	0	Negative	0/6	Negative	0
14	W/60	310.8	No	OA	Aseptic loosening	0	Negative	0/3	Negative	N/A
15	M/55	343.8	No	OA	Instability	0	Negative	1/8 1/8 1/8	CNSMR <i>S. aureus</i> <i>Enterococcus</i> spp	5
16	M/43	254.9	No	OA	Aseptic loosening	0	Negative	0/6	Negative	0

^aComplication treated with revision. ^bThe histologic finding was considered positive for infection when ≥ 5 neutrophils per high-power field (400 x) were found in at least five separate microscopic fields [15]. M = man; W: woman; OA = osteoarthritis; AVN = avascular necrosis; CNSMR = coagulase-negative Staphylococcus resistant to methicillin; CNSMS = coagulase-negative Staphylococcus susceptible to methicillin; N/A = not available.