Identyfikacja bezobjawowych zakażeń okołoprotezowych z zastosowaniem hodowli drobnoustrojów, sonikacji i sekwencjonowania genu 16S rRNA

Identification of asymptomatic periprosthetic infections using microbiological cultures, sonication and 16S rRNA gene sequencing



SAMODZIELNY PUBLICZNY SZPITAL KLINICZNY NR 7 ŚLĄSKIEGO UNIWERSYTETU MEDYCZNEGO W KATOWICACH Górnośląskie Centrum Medyczne im. prof. Leszka Gieca



Przemysław Bereza | Damian Kusz Katedra i Klinika Ortopedii i Traumatologii Narządu Ruchu Śląski Uniwersytet Medyczny w Katowicach



IMPLANT LOOSENING – the scale of the problem

Primary arthroplasty in Poland THA and TKA (2016): **71 122** (base on raport of NFZ)

Revision arthroplasty: 9% hip revision

7% knee revision



PJI: 0.4 - 2,5% - after THA 1- 2% - after TKA





ASEPTIC LOOSENING OF PROSTHESIS

Implant wear particles

Macrophages

Mediators of imflammatory reaction

Osteoclasts activation

Bone resorption Formation of granulation tissue / membrane

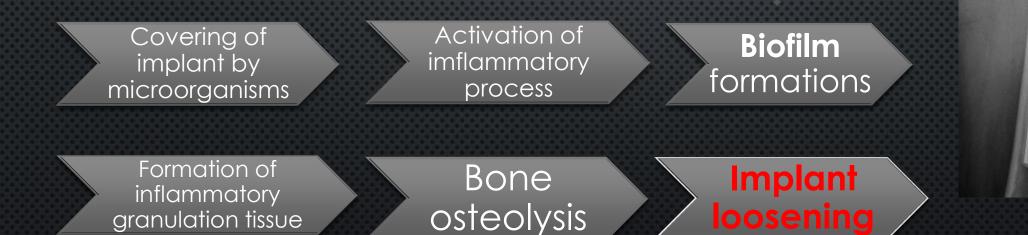
Impant loosening

Enlargement of granulation tissue and atrophy of blood vessels Osteolysis / tissue necrosis



ap

SEPTIC LOOSENING OF PROSTHESIS (PJI)



Definition of periprosthetic joint infection (PJI)

- two positive periprosthetic cultures with phenotypically identical organisms
- a sinus tract communicating with the joint

or when the results of laboratory studies meet at least 3 of 5 diagnostic criteria

- elevated serum CRP and ESR
- elevated synovial WBC count or ++ change on leukocyte esterase test strip
- elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
- positive histological analysis of periprosthetic tissue
- a single positive culture

International Consensus on Periprosthetic Joint Infection MusculoSkeletal Infection Society; MSIS; http://www.msis-na.org/

Hypothesis

Diagnosis of aseptic loosening of the prosthesis does not exclude the presence of bacteria on the surface of the prosthesis.

We postulate that a sonication procedure followed by PCR will improve bacterial identification in non-infected prosthetic joint loosening.

International Orthopaedics (SICOT) DOI 10.1007/s00264-013-1955-9

ORIGINAL PAPER

Identification of silent prosthetic joint infection: pr report of a prospective controlled study

Przemysław L. Bereza · Alicja Ekiel · Aleksandra Auguściak-Duma · Małgorzata Aptekorz · Iwona Wilk · Damian J. Kusz · Piotr Wojciechowski · Gayane Martirosian Bereza et al. BMC Musculoskeletal Disorders (2016) 17:138 DOI 10.1186/s12891-016-0991-1

RESEARCH ARTICLE

Comparison of cultures and 16S rR sequencing for identification of bac two-stage revision arthroplasties: preliminary report

Przemysław Bereza^{1*}, Alicja Ekiel², Aleksandra Auguściak-Duma³, Małgorzata Apti Piotr Wojciechowski¹, Aleksander L. Sieroń³ and Gayane Martirosian^{2,4} BMC Musculoskeletal Disorders RGICAL INFECTIONS

SURGICAL INFECTIONS Volume 18, Number 5, 2017 © Mary Ann Liebert, Inc. DOI: 10.1089/sur.2016.253

> Identification of Asymptomatic Prosthetic Joint Infection: Microbiologic and Operative Treatment Outcomes

Przemysław L. Bereza,¹ Alicja Ekiel,² Aleksandra Auguściak-Duma,³ Małgorzata Aptekorz,² Iwona Wilk,² Piotr Wojciechowski,¹ Damian J. Kusz,¹ and Gayane Martirosian^{2,4}

Main goals of the study



This prospective study was designed to investigate the microbiologic cultures of joint aspiration fluid and intraoperative tissue specimens and to compare the outcomes with sonication fluid cultures in cases supposed pre-operatively to be either aseptic loosening or presumed PJI.

Main goals of the study



Assessment of factors that may increase the risk of loosening elements of joint endoprostheses such as: abnormal body weight, concomitant diseases, previous surgical procedures performed on the examined joints and other operations.

3

Analysis of the impact of body weight and duration of endoprosthesis (endoprosthesis survival) on implant loosening.

Materials and methods

Inclusion criteria:

patients with aseptic hip or knee prosthesis loosening or presumed PJI, who present: clinical signs of prosthesis loosening, radiologic features of loosened implants, normal or elevated concentrations of serum laboratory markers of infection (CRP, ESR, WBC), if there was a lack of or insufficient liquid volume recovered by pre-operative joint aspiration

Exclusion criteria:

signs or symptoms of infection (local inflammatory signs, sinus tract, or systemic symptoms of infection), antibiotic administration two weeks before revision arthroplasty, rheumatoid arthritis, immunosuppression or chemotherapy, and lack of patient consent for participation in the study

Materials and methods

- laboratory markers (serum indicator of infection: WBC, ESR, CRP)
- preoperative culture of synovial fluid from joint aspiration
- intraoperative tissue cultures
- sonification of removed, loosened implants:
 - cultures of sonication liquid
 - molecular techniques: 16S rRNA sequencing
 - in cases of negative culture results
- histopathological analysis of periprosthesis tissues and mebrane on
 - implants (Krenn and Morawietz classification:

type I periprosthetic membrane (ppm) of the wear particle-induced type type II ppm of the infectious type type III ppm of the combined type type IV indeterminate type

Materials and methods

Characteristic of treated patients:

- 37 patients (21 women i 16 men)
- Age: 66.1 y/o (39-81 y/o)
- Operated joints: 30 hips

7 knees

• Time to loosening 110 mos (3-336 mos); ca. 9 y

		Culture	Systemic inflammatory markers				Age of implant	Operative	Type of	
Patient	Joint fluid	Intra-operative specimens					UC	(mos)	procedure	failure
1 2 3	S. aureus S. aureus E. cloacae	S. aureus S. aureus S. epidermidis, S. hominis		Result				3 6 40	Spacer Spacer Spacer	P-atb Arthrodesis None
4 5	E. cloacae S. hominis	S. epidermidis, S. hominis No organism	E. cloacae S. hominis, R. pickettii	N 18.6	N N	+ +		40 36	Partial exchange Spacer	None None
6 7 8 9	No organism No organism No organism No organism	E. faecalis S.epidermidis S.epidermidis No	<i>E. faecalis</i> <i>S. epidermidis</i> No organism	N N N	N N N	+	+ +	48 230 168	Partial exchange Partial exchange Spacer Spacer	None Pih, P-atb None None
10 11 12 13 14	No organism No organism No organism S. epidermidis No organism	The higher cor							al exchange exchange exchange exchange	None None None None None
15 16 17 18 19 20	No organism No organism No organism No organism No organism No organism	patients with bo in one case) or (p=0.005)							S exchange exchange exchange exchange	P-atb Pih, P-atb None None None None
21 22 23 24 25	No organism No organism No organism No organism No organism	The five patient (but with no ob							exchange exchange	Pih, P-atb Pih, P-atb None None None
26 27 28 29 30 31 32 33	No organism No organism No organism No organism No organism No organism No organism No organism	suspected of h						پ ا	exchange exchange exchange exchange exchange exchange nal exchange spacer	None None None None None None None
34 35 36 37	No organism No organism No organism No organism	No organism No organism No organism No organism	No organism No organism No organism No organism	N N N N	N N N N	+++	+ +	138 276 132 192	Partial exchange Partial exchange Partial exchange Spacer	None Pih, P-atb None None

Culture			Systemic inflammatory markers		Type of	Type of prostheses		Operative	Type of	
Patient	Joint fluid	Intra-operative specimens					UC	implant (mos)	procedure	failure
$\frac{1}{2}$	S. aureus S. aureus	S. aureus S. aureus		Result	S			3 6	Spacer Spacer	P-atb Arthrodesis
3	E. cloacae	S. epidermidis, S. hominis		 				40	Spacer	None
4	E. cloacae	S. epidermidis, S. hominis	E. cloacae	N	N	+		40	Partial exchange	None
5	S. hominis	No organism	S. hominis, R. pickettii	18.6	Ν	+		36	Spacer	None
6	No organism	E. faecalis	E. faecalis	Ν	Ν		+	48	Partial exchange	None
7	No organism	S.epidermidis	S. epidermidis	N	N		+	230	Partial exchange	Pih, P-atb
8	No organism	S.epidermidis	No organism	N	N	+		168	Spacer	None
9	No organism	No organism	S. epidermidis	18	15.6	+		96	Spacer	None
10	No organism	No organism	R. pickettii	N	N	+		164	Total exchange	None
11	No organism	No organism	R. pickettii	N	N	+		132	Total exchange	None
12	No organism	No organism	R. pickettii	N	11.3	+		120	Total exchange	None
13	S. epidermidis	No organism	No organism	N	N	+		156	Partial exchange	None
14	No organism	No organism	No organism	N	N	+		17	Spacer	None
15	No organism	No organism	No organism	N	N	+		84	Spacer	P-atb
16	No organism	No organism	No organism	N	N	+		50	Spacer	Pih, P-atb
17	No organism	No organism	No organism	N	N	+		6	Total exchange	None
18	No organism	No organism	No organism	N	N	+		168	Total exchange	None
19	No organism	No organism	No organism	N	N	+		108	Total exchange	None
20	No organism	No organism	No organism	N	N	+		96	Partial exchange	None
21	No organism	No organism	No organism	N	N	+		240	Total exchange	Pih, P-atb
22	No organism	No organism	No organism	N	N	+		120	Total exchange	Pih, P-atb
23	i to organism	ganism	No organism	N	N	-	+	109	Partial exchange	None
23		nism	No organism	N	N		+	132	Partial exchange	None
7		niem	No organism	N	N	+		45	Spacer	None
	Joint liqui	C nism	No organism	N	N		+	120	Partial exchange	None
		nism	No organism	N	N	+		96	Partial exchange	None
1		nism	No organism	N	N	+		98	Partial exchange	None
		niem	No organism	N	N		+	225	Partial exchange	None
PO	sitive cult		No organism	N	N	+		90	Total exchange	None
		nism	No organism	N	N	+		24	Total exchange	None
		nism	No organism	N	N	-	+	140	Partial exchange	None
		nism	No organism	N	N	+		124	Spacer	None
	16.2%	nism	No organism	N	N	-	+	138	Partial exchange	None
		nism	No organism	N	N		+	276	Partial exchange	Pih, P-atb
3		anism	No organism	N	N	+		132	Partial exchange	None
37	No organism		No organism	N	N	+		192	Spacer	None
	and an guine in					-			-1	

Culture			Systemic inflan	matory markers	Type of prostheses		Age of implant	Operative	Type of	
Patient	Joint fluid	Intra-operative specimens	Sonicate	CRP	WBC	С	UC	(mos)	procedure	failure
1	S. aureus	S. aureus	S. aureus	93.4	Ν	+		3	Spacer	P-atb
2	S. aureus	S. aureus	S. aureus	32.5	N	+		6	Spacer	Arthrodesis
3	E. cloacae	S. epidermidis, S. hominis	E. cloacae	39	Ν	+		40	Spacer	None
4	E. cloacae	S. epidermidis, S. hominis	E. cloacae	Ν	Ν	+		40	Partial exchange	None
	S. hominis	No organism	S. hominis,	18.6	Ν	+		36	Spacer	None
		0	R. pickettii						1	
6	No organism	E. faecalis	E. faecalis	Ν	Ν		+	48	Partial exchange	None
	No organism	S.epidermidis	S. epidermidis	Ν	Ν		+	230	Partial exchange	Pih, P-atb
	No organism	S.epidermidis	No organism	N	Ν	+		168	Spacer	None
	No organism	No organism	S. epidermidis	18	15.6	+		96	Spacer	None
	No organism	No organism	R. pickettii	N	Ν	+		164	Total exchange	None
	No organism	No onconions	R. pickettii	N	N	+		132	Total exchange	None
12	No organism		R. pickettii	N	11.3	+		120	Total exchange	None
13	S. epidermid	Intraoperative	lo organism	N	N	+		156	Partial exchange	None
14	No organism		lo organism	Ν	Ν	+		17	Spacer	None
15	No organism	specimens	o organism	Ν	Ν	+		84	Spacer	P-atb
	No organism	specificits	lo organism	Ν	Ν	+		50	Spacer	Pih, P-atb
	No organism		lo organism	N	N	+		6	Total exchange	None
18	No organism		lo organism	N	N	+		168	Total exchange	None
19	No organism	Positive culture	lo organism	N	N	+		108	Total exchange	None
	No organism		lo organism	N	N	+		96	Partial exchange	None
21	No organism		lo organism	N	N	+		240	Total exchange	Pih, P-atb
22	No organism	18.9%	lo organism	N	N	+		120	Total exchange	Pih, P-atb
23			lo organism	N	N		+	109	Partial exchange	None
2			No organism	N	N		+	132	Partial exchange	None
1	I - 9 I I99	-	No organism	N	N	+		45	Spacer	None
1	Joint liqui	0 nism	No organism	N	N		+	120	Partial exchange	None
1		nism	No organism	N	N	+		96	Partial exchange	None
1		nism	No organism	N	N	+		98	Partial exchange	None
		nism	No organism	N	N		+	225	Partial exchange	None
	sitive cult	Ure nism	No organism	N	N	+		90	Total exchange	None
-		nism	No organism	N	N	+		24	Total exchange	None
1	16.2%	nism	No organism	N	N		+	140	Partial exchange	None
1		nism	No organism	N	N	+		124	Spacer	None
1			No organism	N	N		+	138	Partial exchange	None
1		nism	No organism	N	N		+	276	Partial exchange	Pih, P-atb
36		anism	No organism	N	N	+		132	Partial exchange	None
37	No organism	wo organism	No organism	N	N	+		192	Spacer	None
	_									

C = cemented; CRP = C-reactive protein; N = normal value (CRP: N < 10 mg/L; WBC: N < $10,000/\text{mm}^3$); P-atb – prolonged antibiotic therapy, Pih = prolonged incision healing; UC = uncemented; WBC = white blood cell

Culture		5	vstemic infla	mmatory markers	Type of	Type of prostheses		Operative	Type of	
Patient	Joint fluid	Intra-operative specimens	Sonicate	CRP	WBC	С	UC	implant (mos)	procedure	failure
1 2 3 4 5	S. aureus S. aureus E. cloacae E. cloacae S. hominis	S. aureus S. aureus S. epidermidis, S. homi S. epidermidis, S. homi No organism	Sonicatio	n	N N N N	+ + + +		3 6 40 40 36	Spacer Spacer Spacer Partial exchange Spacer	P-atb Arthrodesis None None None
10 11	No organism No organism No organism No organism No organism No organism No organism	E. faecalis S.epidermidis S.epidermidis No organism No organism	Positive cult		N N 15.6 N N 11.3	+ + + +	+ +	48 230 168 96 164 132 120	Partial exchange Partial exchange Spacer Total exchange Total exchange Total exchange	None Pih, P-atb None None None None None
13 14 15 16	S. epidermid No organism No organism No organism No organism No organism	Intraoperative specimens	o organism o organism o organism o organism o organism	N N N N N	N N N N N N	+ + + + +		156 17 84 50 6 168	Partial exchange Spacer Spacer Total exchange Total exchange	None None P-atb Pih, P-atb None None
19 20 21	No organism No organism No organism No organism	Positive culture 18.9%	lo organism lo organism lo organism lo organism lo organism lo organism	N N N N N	N N N N N	+ + + +	+++++	108 96 240 120 109 132	Total exchange Partial exchange Total exchange Total exchange Partial exchange Partial exchange	None None Pih, P-atb Pih, P-atb None None
	Joint liqui sitive cult	nism nism	No organism No organism No organism No organism No organism No organism	N N N N N N	N N N N N	+ + +	+ +	45 120 96 98 225 90	Spacer Partial exchange Partial exchange Partial exchange Partial exchange Total exchange	None None None None None
1	16.27	nism	No organism No organism No organism No organism No organism No organism No organism	N N N N N N N N N	N N N N N N N	+ + + +	+ + +	24 140 124 138 276 132 192	Total exchange Partial exchange Spacer Partial exchange Partial exchange Partial exchange Spacer	None None None None Pih, P-atb None None

		Culture	Sust	temic infla	ammatory markers	Type of p	prostheses	Age of implant	Operative	Type of
Patient	Joint fluid	Intra-operative specimens	Sonicate	CRP	WBC	С	UC	(mos)	procedure	failure
1 2 3 4 5	S. aureus S. aureus E. cloacae E. cloacae S. hominis	S. aureus S. aureus S. epidermidis, S. homi S. epidermidis, S. homi No organism	Sonication		N N N N	+ + + +		3 6 40 40 36	Spacer Spacer Spacer Partial exchange Spacer	P-atb Arthrodesis None None None
6 7 8 9 10 11 12 13	No organism No organism No organism No organism No organism No organism S. epidermid	E. faecalis S.epidermidis S.epidermidis No organism No organism	Positive cultu 29.7%		N N 15.6 N N 11.3 N	+ + + + +	+ +	48 230 168 96 164 132 120 156	Partial exchange Partial exchange Spacer Spacer Total exchange Total exchange Total exchange Partial exchange	None Pih, P-atb None None None None None
14 15 16 17 18 19 20 21 22 23 2	No organism No organism No organism No organism No organism No organism No organism No organism No organism	specimens Positive culture 18.9%	lo organism lo organism	N N N N N N N N N N N	- a larg cases.		ety of k	pacteri	ia in each was CNS	
	Joint liqui sitive cult	nism nism	No organism No organism No organism No organism No organism No organism	N N N N N N N		her rep	present	tatives	of human	and
3	16.27		No organism No organism No organism No organism No organism No organism	N N N N N N	N N N N N	+ + +	+ + +	140 124 138 276 132 192	Partial exchange Spacer Partial exchange Partial exchange Partial exchange Spacer	None None Pih, P-atb None None

		Culture Systemic inflammatory markers Ty		Type of prostheses Age of implant		Age of	Operative	Type of		
Patient	Joint fluid	Intra-operative specimens	Sonicate	CRP	WBC	С	UC	(mos)	procedure	failure
1 2 3 4 5	S. aureus S. aureus E. cloacae E. cloacae S. hominis	S. aureus S. aureus S. epidermidis, S. hominis S. epidermidis, S. hominis No organism	S. aureus S. aureus E. cloacae E. cloacae S. hominis, R. pickettii	93.4 32.5 39 N 18.6	N N N N	+ + + +		3 6 40 40 36	Spacer Spacer Spacer Partial exchange Spacer	P-atb Arthrodesis None None None
6 7 8 9 10	No organism No organism No organism No organism No organism	E. faecalis S.epidermidis S.epidermidis	<i>E. faecalis</i> <i>S. epidermidis</i> No organism	N N N	N N N	+	+ +	48 230 168	Partial exchange Partial exchange Spacer Spacer Total exchange	None Pih, P-atb None None None
10 11 12 13 14 15 16 17 18 19 20 21 22 23	No 01 No 01 <i>S. epi</i>	Percentage of n comparison		ard mic	robiologi				Total exchange Total exchange Partial exchange Spacer Spacer Total exchange Total exchange Total exchange Partial exchange Total exchange Total exchange Total exchange Partial exchange Partial exchange	None None None P-atb Pih, P-atb None None None Pih, P-atb Pih, P-atb None
24 25	No organism No organism	No organism No organism	No organism No organism	N N	N N	+	+	132 45	Partial exchange Spacer	None
26 27 28	No organism No organism No organism	No organism No organism No organism	No organism No organism No organism	N N N	N N N	+++	+	120 96 98	Partial exchange Partial exchange Partial exchange	None None None
29 30	No organism No organism	No organism No organism	No organism No organism	N N	N N	+	+	225 90	Partial exchange Total exchange	None None
31 32 33	No organism No organism No organism	No organism No organism No organism	No organism No organism No organism	N N N	N N N	+ +	+	24 140 124	Total exchange Partial exchange Spacer	None None None
34 35 36 37	No organism No organism No organism No organism	No organism No organism No organism No organism	No organism No organism No organism No organism	N N N	N N N N	+ +	+ +	138 276 132 192	Partial exchange Partial exchange Partial exchange Spacer	None Pih, P-atb None None

The outcomes of histopathologic tests of peri-prosthetic tissues

 infection type II - in all culture-positive joints (patients no 1-8) p=0.004
 infection type II - in 41.4% of the cases with

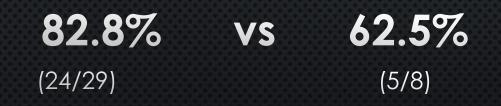
negative culture results

type I periprosthetic membrane (ppm) of the wear particle-induced type type II ppm of the infectious type type III ppm of the combined type type IV indeterminate type

Loosening of implants was noted more often in patients with:

- BMI > 25 (overweight and obese) and
- negative cultures results

than in the group of patients with positive culture result.



(correlation was not statistically significant)

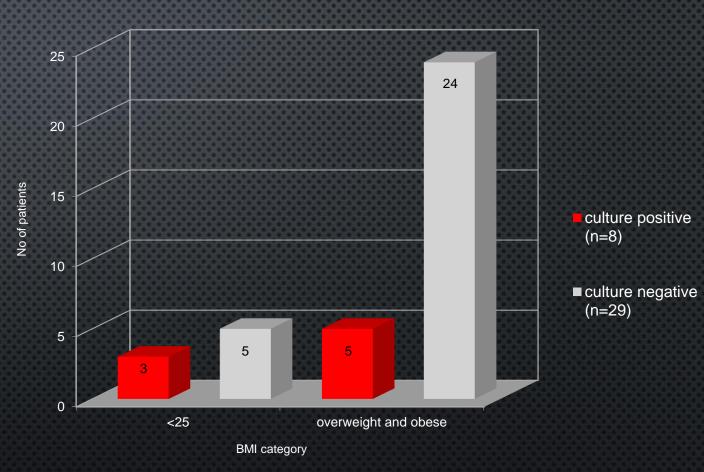


FIG. The distribution of BMI in group of patients with positive (n = 8) and negative (n = 29) culture results.

- Previous orthopaedic operations (not only of the examined joints) and
 Cardiac diseases (mostly)
- Cardiac diseases (mostly ischemic heart disease)

were significantly more common in patients with positive cultures results.

(p=0.04)

Comorbiances.	
Cardiac diseases	19/37 (51%)
Previous operations	15/37 (40%)
Previous other joints replacement	13/37 (35%)
Digestive diseases	10/37 (27%)
Previous operation of the affected joint	8/37 (22%)
Previous revision surgeries of the joint(s)	7/37 (19%)
Thyroid disease (hyperthyroidism)	6/37 (16%)
Diabetes melitus	4/37 (11%)
Nicotine addiction	4/37 (11%)
Respiratory system diseases	3/37 (8%)
Arthropaties	3/37 (8%)

Comorbidities:

Implant loosening < 24 months

- in 25% of patients with positive culture results (2/8)
- in 10.3% patients with aseptic (3/29)
- Implant loosening < 6 months
 - in 25% (2/8)
 - **3,5%** (1/29)

Some authors have proved a correlation between prosthesis age and failure risk, in that early loosening is more frequently caused by hidden PJI than is late loosening (>24 mos), 40% vs. 22%, respectively

type II (Tsukayama)- late chronic infections with the origin of symptoms > 1 month after surgery

Table. Complications in Relation to Type of Primary Arthroplasty and Revision Procedure

Turnellinine		Type of revision	Failures	Culture results			
Treated joint and implant	N (%)	surgery for loosened implant	surgery for at two-year — posened implant followup		Negative		
Hip	30 (81)		6	2	4		
Cemented	21 (70)	6 partial revisions	1	1 (case 4)	-		
		10 total revisions	2	_	2 (cases 21 and 22)		
		5 spacers	1		1 (case 16)		
Non-cemented							
Press-fit	5 (16)	5 partial revisions	2	1 (case 7)	1 (case 35)		
Screwable cup	4 (13)	4 partial revisions	-	-	-		
Knee	7 (19)	7 spacers	3	2 (cases 1 and 2)	1 (case 15)		

ONE-STAGE ARTHROPLASTY:

 performed in most patients with pre-operative diagnosis of aseptic loosening : 67% (25/37)

 performed in 76% (22/29) culture negative patients:

 partial exchange :
 41% (12/29)

 total exchange :
 35% (10/29)

TWO-STAGES ARTHROPLASTY

- performed in 12 cases of the entire series; in all patients with PJI highly suspected because of significant elevated CRP
- in 63% patients (5/8) with positive culture
- in **24% of culture-negative patients** with probable peri-prosthetic infection.

Two years' follow-up:

- 9 failures (prolonged antibiotics administration caused by impaired wound healing)
- The complications were more frequent in patients with positive than with negative cultures, 50% and 17.2%, respectively (p = 0.08).
- The complications were more frequent in patients operated with 2-stage procedure
- Failures were observed in 42.8% of the treated knees

20% of the treated hips

In two cases of likely PJI, the patients required re-operation:

- 1st case (patient no. 1): prolonged antibiotic therapy as well as surgery resurfacing of the patella

 it was not considered a failure
- 2nd case (patient no. 2): finally underwent arthrodesis of the knee because of
 the general medical condition and the high risk of re-infection



Conclusion 1.

We found micro-organisms on the surface of implants removed because of clinical features of aseptic loosening of prosthesis. Inclusion of the sonication procedure in the diagnostic algorithm of prostheses loosening increases the ability to identify pathogens.

Conclusion 2.

Previous operations and heart disease are more common than other co-morbidities and probably have a greater influence on implant loosening.



Conclusion 3.

The results of this study suggest the co-existing roles of the BMI and the period to implant loosening as well as biologic agents in process of prostheses loosening.

Conclusion 4.

Our analysis proved better outcomes of operative treatment of aseptic loosening and presumed PJI using one-stage operations than two-stage revision arthroplasty.

THANK YOU FOR ATTENTION!



RAUMA

SAMODZIELNY PUBLICZNY SZPITAL KLINICZNY NR 7 ŚLĄSKIEGO UNIWERSYTETU MEDYCZNEGO W KATOWICACH Górnośląskie Centrum Medyczne im. prof. Leszka Gieca



DEDIA I TA

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