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ORIGINAL STUDY

Variety in diagnosis and treatment of periprosthetic joint infections in Belgium and the Netherlands

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Recently, guidelines regarding diagnosis and treatment of periprosthetic joint infection (PJI) have been published, but it is unknown how well these are followed in the Netherlands and Belgium. Therefore, a survey study was performed in the Netherlands and Belgium.

81 orthopedic departments responded (54% in the Netherlands, 52% in Belgium). The majority used protocols for antibiotic and surgical treatment. To discriminate between early and late infection, differences in periods used were seen between respondents, and between countries. Empirical antibiotic treatment varied greatly. Debridement, antibiotics, irrigation and retention of the prosthesis (DAIR) is the almost unanimous treatment of choice for early PJI.

Guidelines are available, but seem not (yet) to be followed accurately, and do not have answers to all possible treatment options. Perhaps, national guidelines might produce more standardized care, and consequentially, easier comparison for research, more transparency for patients, and less health care costs.

Keywords : periprosthetic joint infection ; infection ; prosthetic ; arthrosplasty.

INTRODUCTION

With the absolute increase in THA and TKA performed each year (*13*), a rise in (absolute) number of complications can be expected. Of these, periprosthetic joint infection (PJI) is one of the most devastating complications. Whether the treatment consists of chronic antibiotic use, multiple debridement procedures, one- or two-stage revision or even a Girdlestone procedure, long term hospital stay and surgery are required in most cases (*17*).

According to the National Institute for Public Health and the Environment in the Netherlands (*16*), in 2013 approximately 100.000 THAs and 70.000 TKAs were performed. With a PJI rate of 1.8 and 1.3%, respectively, a total number of around 2700 hip and knee PJIs were seen. When also counting infections of revision knee and hip arthroplasty and hip hemiarthroplasty, this adds up to approximately 3700 PJIs, yearly, in the Netherlands.

Revision arthroplasty for PJI costs around 30.000 euro per patient for THA (*10,13*), and around 25.000 euro per patient for TKA (*13*). So, in the Netherlands

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alone, the total costs of knee and hip PJIs are approximately 100 million euro yearly. Therefore, treatment should be optimized, thus minimizing total costs (*10*). To optimize treatment, the best possible evidence needs to be made public, for example by (national/international) guidelines. Plus, standardization would also aid comparison of different treatment options.

Just until recently, the first real guidelines have been published (*17*), and soon the results of international efforts to reach consensus will be made public. Still, as it is seen more often in health care, we believe that these advices have not yet transuded to hospital protocols and individual doctors. To test this hypothesis, and to raise awareness for treating patients with PJI with the best evidence based medicine, a survey study was performed.

METHODS

In March 2013 a survey regarding the treatment of PJIs was sent to all orthopedic departments in the Netherlands and Belgium. A total of 152 orthopedic surgery departments in the Netherlands and Belgium were contacted. In the following months, all departments that had not responded were asked again twice to respond, first by email, and secondly by a telephone call.

The survey was an online questionnaire, and could be completed within 10-15 minutes. It was designed by the leading author, and after redaction by all other authors agreed upon and published. It was divided in three parts : demographics and protocols, diagnostics, and antibiotic and surgical treatment, all of which contained approximately 10 questions. For most questions, an "other" box was added, for free text. In table I the subjects questioned are listed.

Table I. — Subjects questioned in the survey

Demographics and protocols	Type of hospital
	Number of THAs performed in 2012
	Number of TKAs performed in 2012
	Number of hip PJIs in 2012
	Number of knee PJIs in 2012
	Percentage of PJIs referred to your hospital by others
	Multidisciplinary meeting for PJI treatment
	Is a set protocol used for antibiotic treatment of PJIs ?
	Is a set protocol used for surgical PJI treatment ?
Diagnostics and antibiotic treatment	Diagnostic tools used for PJI diagnosis
	Where is aspiration performed in case of suspected hip PJI ?
	Where is aspiration performed in case of suspected knee PJI ?
	What threshold is used to discriminate between early and late PJI ?
	Which antibiotic agent is used for empirical therapy (when the causative microorganism is yet unknown) ?
	Is additional rifampin added to therapy ?
	Is the antibiotic therapy changed according to culture results ?
	What is the minimal total period of antibiotic treatment ?
Surgical treatment	What kind of surgical treatment is performed for early PJI ?
	What kind of surgical treatment is performed for late PJI ?
	Is a set criterion used to choose between DAIR and implant removal ?
	Is a set number of DAIR procedures used ?
	If any, what local antibiotic treatment is used in DAIR procedures ?
	Are exchangeable components always exchanged ?
	If any, what local antibiotic treatment is used in implant removal surgery ?
	What period is used between removal and reimplantation in staged revision ?

Abbreviations : THA : Total Hip Arthroplasty ; TKA : Total Knee Arthroplasty ; PJI : Periprosthetic Joint Infection ; DAIR : Debridement, Antibiotics, Irrigation and Retention of the prosthesis.

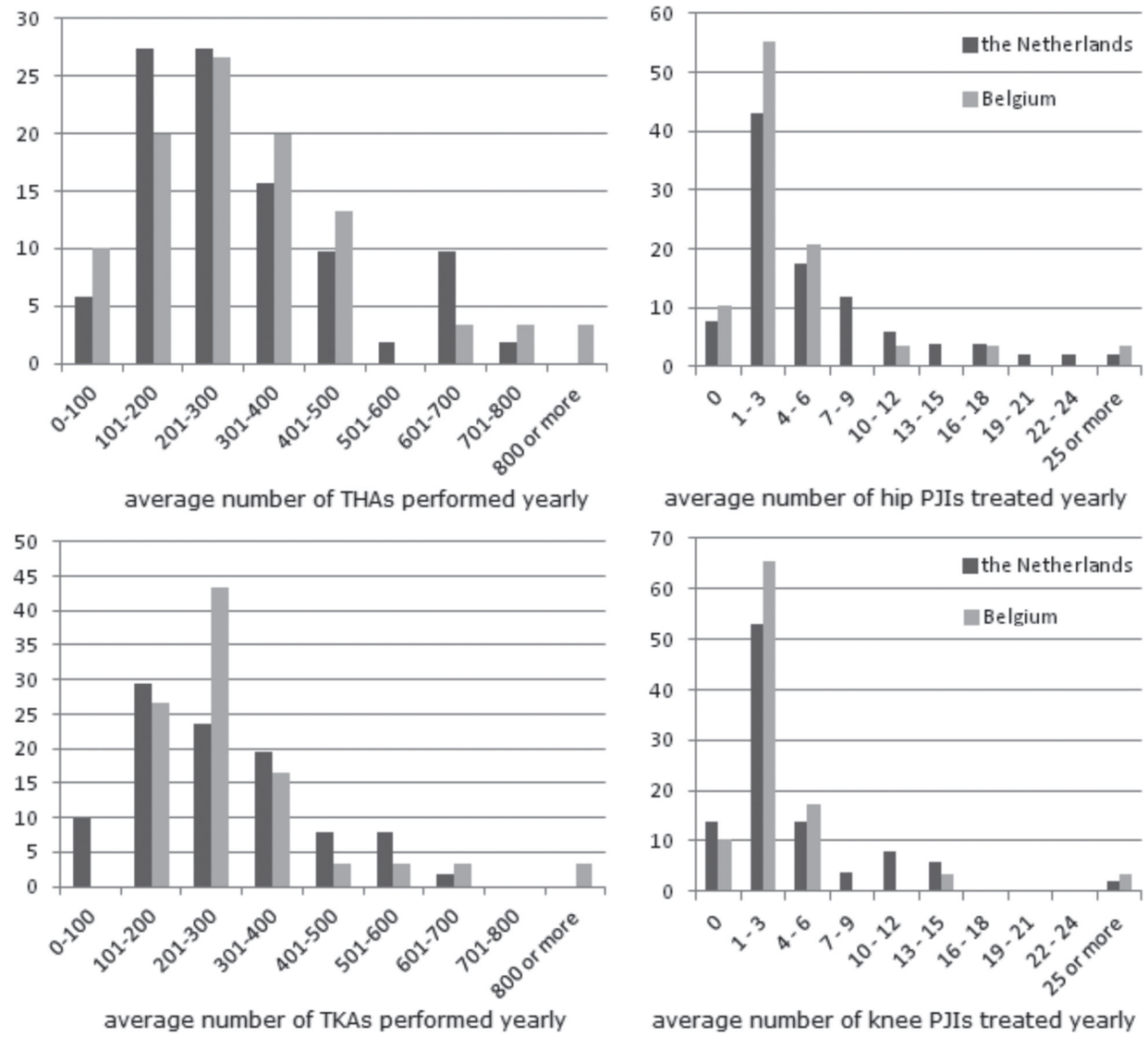

Fig. 1a-d. — Demographics of the respondents, in annual number of THAs (1a), TKAs (1b), hip PJIs (1c) and knee PJIs (1d) (percentages).

RESULTS

In total, 81 orthopedic departments responded to the survey : 51 in the Netherlands (54% response), and 30 in Belgium (52%). Of the Dutch responses, 44% were from teaching hospitals (17% university hospitals), versus 86% in Belgium (6% university hospitals).

Per year, most Dutch hospitals perform between 101 and 400 THAs and TKAs (71% and 73%, respectively). In Belgium, between 101 and 400 THAs and TKAs are performed in 67% and 87% of the hospitals, respectively. The most hospitals treat 1-3 hip and knee PJIs on a yearly base. The number of THAs and TKAs, as well as the number of infections are shown in figure 1.

Table II. — Percentages of multidisciplinary and standardized care for PJI treatment in the Netherlands and Belgium

	the Netherlands	Belgium
Multidisciplinary approach		
None	38%	47%
With a microbiologist	35%	19%
With an infectiologist	2%	6%
With both	16%	3%
Other	2%	6%
No answer	*7%*	*19%*
Use of protocol		
Regarding the use of antibiotics	87%	76%
Regarding surgical treatments	77%	59%

When asked for the percentage of PJI patients that are referred to the responding surgeon, the largest group have few referrals : 44% of the Dutch, and 28% of the Belgian respondents have 0-10% referred patients. The second largest group, however, have 90-100% referred patients : 16% and 17%, respectively.

A multidisciplinary approach for PJI treatment is standard care in 55% of the Dutch hospitals and 33% of the Belgian hospitals. In both countries, this usually involves a medical microbiologist.

Protocols for antibiotic and surgical treatment do exist in most hospitals, slightly more in the Netherlands. Here, antibiotic and surgical treatment is standardized in 87% and 77% of the hospitals, versus 76% and 59% in Belgium, respectively (Table II).

The usage of possible methods to diagnose PJI are listed in figure 2. C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), leukocyte count, X-ray, and intra-operative tissue cultures are almost always performed in both countries (more than 80% responded “always”). In Belgium, intra-operative swab cultures, aspiration leukocyte count, aspiration culture and serum leukocyte count are also almost always performed, which is less in the Netherlands. Arthrography is almost never performed in Belgium, but sometimes in the Netherlands. Sonication of prosthetic material is either always performed (10% in the Netherlands, 20% in Belgium), or not at all (80% and 70%, respectively).

For PJI diagnosis, almost every hospital performs standard joint aspiration. A difference between the countries is seen regarding suspected hip PJIs. In Belgium, aspiration is almost always performed in the operating room. In the Netherlands, this is also done at the radiology department by either a radiologist or orthopedic surgeon. When knee PJI is suspected, two thirds of the patients are aspirated at the outpatient clinic, and one third in the operating room. This is the same in both countries (Fig. 3).

Only few hospitals always perform all the tests that are mentioned in the definition of PJI diagnosis : only 6% of the Dutch and 18% of the Belgian respondents always perform CRP, ESR, aspiration leukocyte count, cultures and histology (*23*).

When asked for a threshold to discriminate between early and late infection, more than half of the Dutch respondents use six weeks postoperatively, and another 36% three months. In Belgium, this is spread out between 2 weeks and six months, with a peak at three months (44%) (Fig. 4).

Antibiotic treatment differs between the two countries. In Belgium, as empirical treatment, mostly amoxicillin/clavulanate or a combination of agents is given (21% and 31%, respectively), whereas in the Netherlands flucloxacillin and cephalosporins are more commonly used (28% and 36%, respectively). Adjuvant therapy with rifampin is frequently used in the Netherlands, and seems a bit

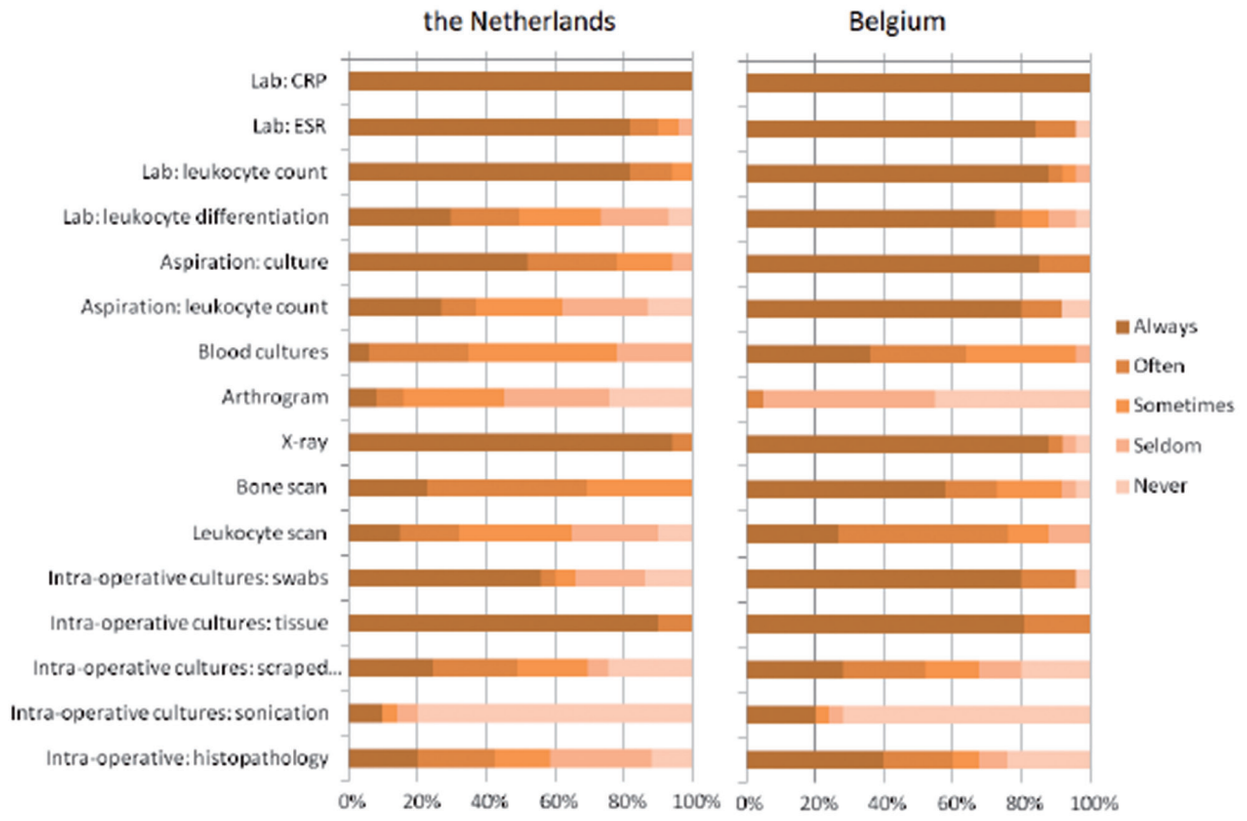

Fig. 2. — Diagnostic methods used for PJI diagnosis. Abbreviations : CRP : C-reactive protein ; ESR : Erythrocyte Sedimentation Rate.

less used in Belgium. Adaptation of the antibiotic regiment is always done in consultation, usually after consulting the microbiologist (Table III).

Early PJIs are almost always treated with debridement, antibiotics, irrigation and retention of the prosthesis (DAIR) in both countries. One-stage revision, two-stage revision and the (chronic) use of antibiotics only are far less used. Remarkably, treatment with antibiotics only is still used in around 15% of all cases of both early and late PJI in Belgium. In the Netherlands, this is much less used, approximately 5%. The same kinds of results are shown for one- and two-staged revision for early PJI : 15% in Belgium, 5% in the Netherlands.

For late PJI, two-stage revision is most frequently used, but in a substantial part DAIR is also tried (always or often in 40% in the Netherlands, and 20% in Belgium). One-stage revision and antibiotics only seem less favorite in both countries, and are more or less equally used for early and late infections (Fig. 5).

In most hospitals, the criterion to choose between DAIR and removal of the prosthesis for one- or two-stage revision is not well-defined, and a personal choice for each patient (based on different clinical symptoms) is made by approximately half of the respondents (50% in the Netherlands, 44% in Belgium). Other hospitals are more strict in their decision and use a selected time after primary surgery (25 and 37%, respectively), symptom duration (6 and 7%, respectively), loosening of the prosthesis (6 and 3%, respectively), or “other reasons”,

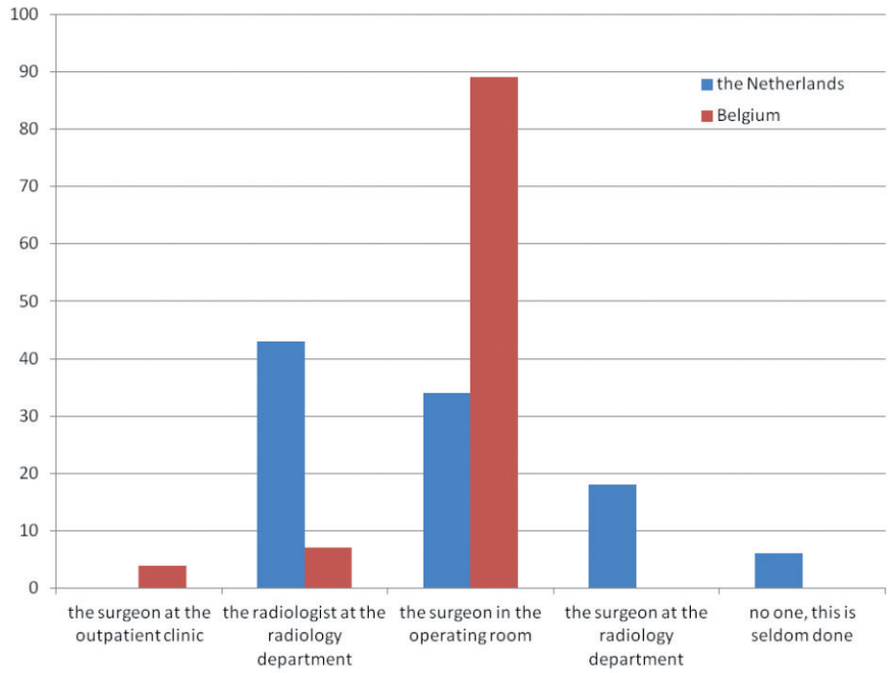

Fig. 3a. — Methods of sterile joint aspiration of the hip for PJI diagnosis, in percentages

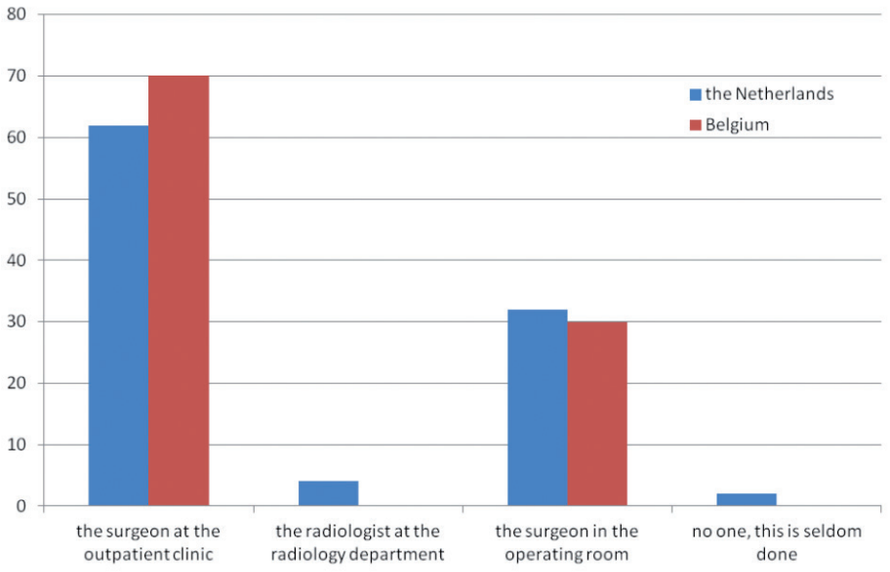

Fig. 3b. — Methods of sterile joint aspiration of the knee for PJI diagnosis, in percentages

usually a combination of the previous mentioned reasons (13 and 7%, respectively).

If DAIR is performed, the number of DAIR procedures attempted varies significantly between respondents. A fixed number (either always one, always two or always three procedures) is used by the minority in the Netherlands. In Belgium on contrary, a fixed number is used by 12%, but this is

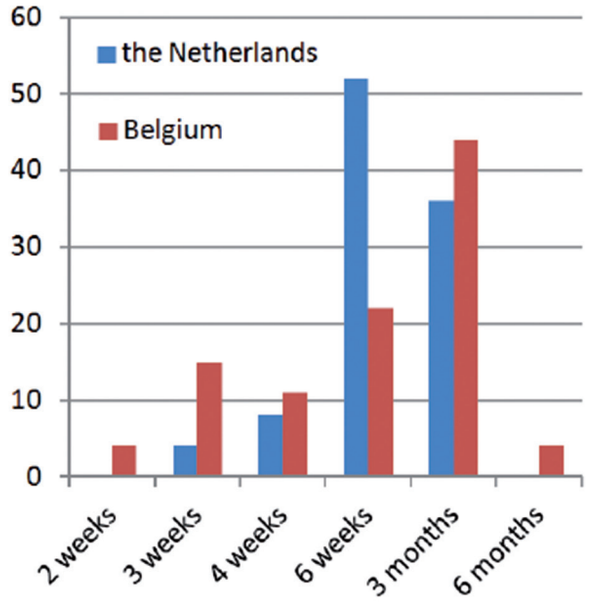

Fig. 4. — Threshold used for early versus late PJI, in percentages.

always one try. When a variable number of procedures is used, 46% of the Dutch respondents and 24% of the Belgians wield a maximum number of DAIR procedures, usually 2 or 3 attempts. Some hospitals are guided by the negative cultures found in the previous procedure(s) (12 and 14%, respectively).

The exchange of modular components during DAIR procedure is much higher in Belgium (77% always, 15% sometimes) than in the Netherlands (41% always, 35% sometimes). For DAIR treatment, local antibiotic carriers are used by 88% of the Dutch, and 73% of the Belgium respondents. In both countries, 38% of the respondents use an antiseptic or antibiotic agent for irrigation. After prosthesis removal, beads and sponges are more frequently used in the Netherlands, whereas the Belgians obviously prefer spacers (Table IV).

After removal of the prosthesis, the interval period used before reimplantation differs between the two countries : the Dutch use either six weeks or three months in most hospitals, the Belgian respondents use six weeks in half of the hospitals, but a third based this on other parameters, such as serum

Table III. — Use of antibiotic agents in PJI treatment, in percentages; *: with or without the use of rifampin

Empirical antibiotic treatment*	the Netherlands	Belgium
Amoxicillin/clavulanate	8	21
Flucloxacillin	28	10
Vancomycin	6	10
Cefuroxime	18	0
Cefazolin	14	7
Ceftriaxone	4	0
Clindamycin	4	0
Ciprofloxacin	2	0
Amikacin	0	3
Combination therapy	10	31
Flucloxacillin/vancomycin	*4*	*3*
Ciprofloxacin/vancomycin	*2*	*0*
Gentamicin/vancomycin	*2*	*0*
Amikacin/vancomycin	*2*	*0*
Flucloxacillin/gentamicin	*0*	*10*
Flucloxacillin/amikacin	*0*	*7*
Cefazolin/ciprofloxacin	*0*	*3*
Cefazolin/amikacin	*0*	*3*
Clindamycin/ciprofloxacin	*0*	*3*
In consultation with a microbiologist	6	10
“Broad spectrum”	0	3
Cefalosporin	0	3
Rifampin use		
Always	12	3
Often	31	17
Sometimes	10	41
Seldom	3	7
Never	2	0
Later, based on culture results	26	21
Other	16	10
Adaptation of antibiotic treatment based on culture results		
Use of a set protocol	0	0
In consultation with a medical microbiologist	86	78
In consultation with an infectiologist	2	15
In consultation with both	12	7
Without consultation	0	0
No adaptation	0	0
Other	0	0

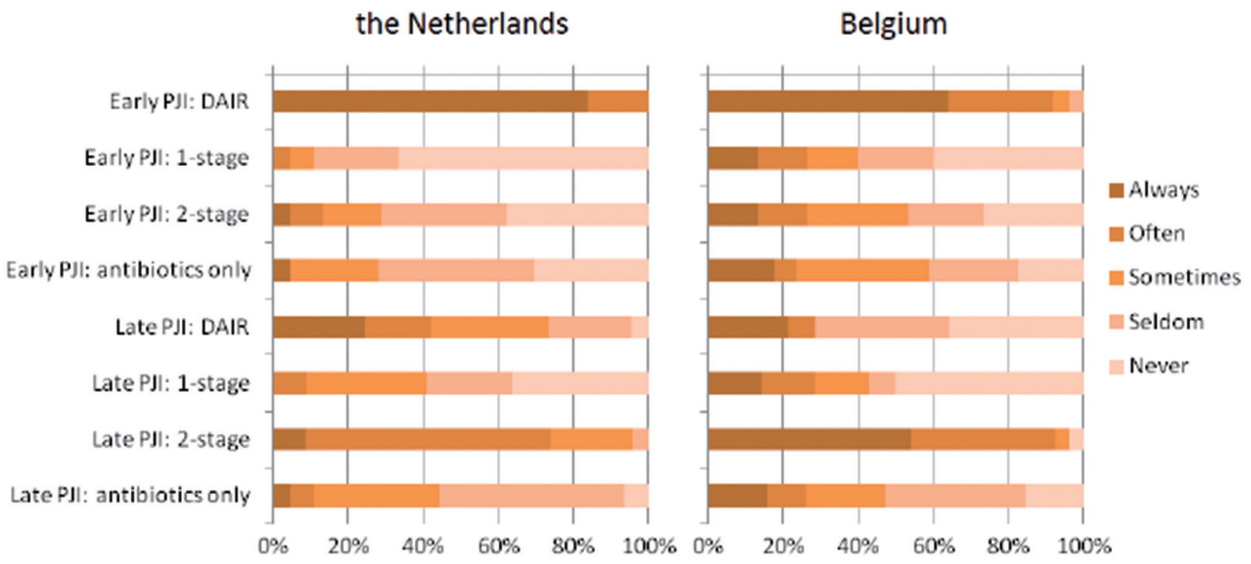

Fig. 5. — Treatment methods used for early and late PJI. Abbreviations : DAIR : Debridement, Antibiotics, Irrigation and Retention of the prosthesis.

Table IV. — Fixed number of procedures used or not used when DAIR is performed, in percentages

Is a fixed number of DAIR procedures used?	The Netherlands	Belgium
Yes, 1	2%	12%
Yes, 2	4%	0%
Yes, 3	2%	0%
No, 1 or 2 (maximum 2)	18%	8%
No, 1,2 or 3 (maximum 3)	22%	12%
No, 1,2,3 or 4 (maximum 4)	2%	0%
No, 1,2,3,4 or 5 (maximum 5)	2%	0%
No, but a maximum is used (number not given)	2%	4%
No, this is guided by negative cultures after the last procedure	6%	0%
No, this is guided by negative cultures after the 2 last procedures	2%	0%
No, this is guided by negative cultures (number of times not mentioned)	6%	12%
No (not further specified)	31%	54%

infection protein levels and clinical symptoms (Fig. 6).

DISCUSSION

Although the most respondents state to use a standardized treatment protocol, for both the medical and surgical treatment of PJI, the answers to most questions are not unambiguously. For such a severe complication, treatment should be optimal for each patient, and according to the latest evidence. Unfortunately, the evidence for many diagnostic tools and treatment options is poor and uncertain ; for diagnosis and surgical treatment, no randomized controlled trials exist, and only a few exist for antibiotic treatment (*17*).

For PJI diagnosis, the IDSA-guideline mentions the utility of ESR, CRP, X-ray, pre-operative

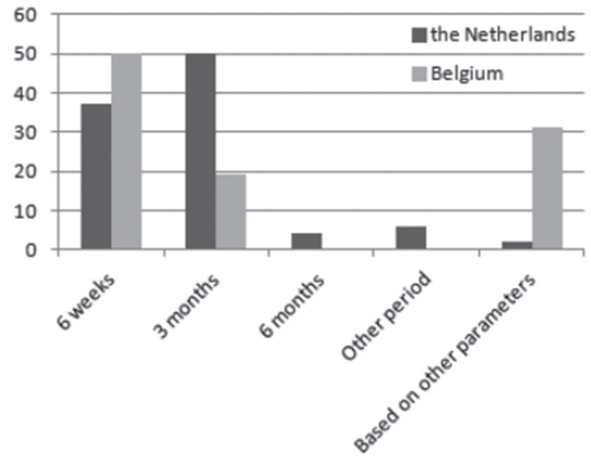

Fig. 6. — Minimum period until reimplantation is performed after removal surgery for PJI, in percentages.

aspiration, blood cultures, intraoperative histology and intra-operative cultures (*17*). Of these 7 test methods, 3 are not routinely used in both countries : aspiration (especially in the Netherlands), blood cultures and histology. Only a minority of the respondents perform all tests to possibly fulfil these minor criteria (6% in the Netherlands, 18% in Belgium).

The latest criteria for PJI diagnosis, as agreed upon during the 2013 consensus meeting, are as follows (*23*) :

- Two positive periprosthetic cultures with phenotypically identical organisms, or
- A sinus tract communicating with the joint, or
- Having three of the following minor criteria :
  - Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
  - Elevated synovial fluid white blood cell (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

The use of additional imaging (bone scan, leukocyte scan) has only a limited role in PJI diagnosis (*17,23*), but it is used "always" by 15-55% of the respondents.

Location and performing physician of joint aspiration (arthrocentesis) differs between the countries and the affected joints. The most optimal way to perform aspiration for PJI diagnosis is not mentioned by other authors, but perhaps this is less relevant than the most important issue : it should be as sterile as possible, and true joint fluid should be aspirated.

A big difference is seen in the threshold surgeons wield between early and late infection between the two countries, but also between the respondents. Of course, the different classification systems play a role in this difference : Tsukayama describes 4 post-operative weeks, Toms adapted this to 6 weeks, and the Zimmerli classification uses 3 months (*19,20,22*). Additionally, to choose between DAIR treatment or implant removal, the IDSA guidelines advise a threshold of 30 days or 3 weeks of PJI symptoms (*17*).

The Belgians tend towards a 3 months threshold between early and late PJI. The Dutch, on average, use a shorter period (more claim to use 6 weeks). The reason of this difference is difficult to ascertain. Perhaps the Zimmerli classification is used more often in Belgium (*22*). Whether the difference has a clinical consequence and affects patient outcome is unknown.

Empirical antibiotic treatment differs extremely between respondents. In the Netherlands, there is a tendency to use smaller spectrum antibiotic agents (e.g. flucloxacillin instead of amoxicillin/clavulanate). This may be because the Netherlands are known for their low antibiotic subscription rate (*2*). No advice is given in current guidelines (*17*), but one Portuguese study advises the use of vancomycin for PJI caused by an unknown micro-organism (*18*). In our population, vancomycin was used by 13-16% of the respondents, either alone or in combination.

The additional use of rifampicin is more widely studied and recommended by most (*17,22*), at least when not all foreign material is removed. The answers of the respondents vary, but this may be due to the fact that we did not differentiate between prosthesis retention and removal.

Although the definition of early PJI is variable, almost all respondents treat this kind of infection

with DAIR. The number of DAIR procedures that is attempted before removal is considered is widely variable, but the Dutch seem to perform more procedures than the Belgians. The number of procedures is not mentioned in the IDSA guidelines (*17*), but various studies state that one debridement procedure with additional procedures on indication seem to have a slightly higher success rate (*4,15,21*). Others claim that standard multiple procedures perform better (*1,7*).

Of the respondents, 12-14% are guided by negative cultures found in the previous procedure(s) to decide whether a next debridement procedure should be performed. This approach is not mentioned in guidelines or reviews (*17,22*), and to our knowledge, no evidence exists that this should be a factor in treatment choice.

Deciding performing either DAIR or removal (for one- or two-stage revision) is not well defined, and depends on several different factors, such as time after initial arthroplasty, symptom duration and prosthesis loosening (*17,22*). However, the majority makes a weighted decision for each individual patient.

The exchange of modular components is more commonly performed in Belgium than in the Netherlands. Nevertheless, there are still respondents in both countries that do not always exchange components after debridement and irrigation. Several studies have shown that retention of these parts has worse outcome (*6,14*), and the IDSA guidelines advise against it (*17*).

The use of local antibiotic treatment is relatively common in the Netherlands and Belgium (88% and 73%). The evidence for or against local treatment is poor, and the choice of local carrier seems debatable ; beads have a longer lasting but lower concentration of antibiotics, and can become a carrier of microorganisms themselves (*5*). Sponges reach a higher concentration in a shorter period, and do not need removal surgery, but may cause more wound secretion (*11*).

For late PJI, two-stage revision is performed the most. One-stage has as smaller, but significant role in both countries. Why one-stage revision was sometimes chosen over two-stage was not asked, but this may be based on preference of the performing surgeon. In both countries, DAIR is performed for late PJI as well. Results after DAIR treatment for late chronic PJI are poor, but for acute hematogenous PJI, which can occur up to years after initial arthroplasty, the results may be good (*12*).

As for local antibiotic treatment after prosthesis removal, many options were mentioned. In Belgium, most respondents use spacers, while the Dutch seem to use all options mentioned about equally (spacers, beads, sponges). The use of spacers may cause less functional problems for the patient, but this is not well studied (*17*).

The minimum period until reimplantation is usually at least 6 weeks, and the Dutch seem to use at least 3 months in most cases. To our knowledge, no evidence exists to support either period.

Regarding the use of antibiotic agents, the guidelines advise 4-6 weeks of antibiotic treatment, and subsequently 2-8 extra weeks without antibiotics (*17*). It is also advised to use clinical parameters such as CRP to guide the reimplantation period (*17*), something that seems to be used more in Belgium than in the Netherlands.

This study clearly indicates the variety of diagnostic options and treatments performed for PJI. However, approximately half of all hospitals responded to the survey, which may have caused bias : it is uncertain whether the other hospitals would have given other answers. Nevertheless, it is improbable they would have given the straight and unanimous answers that would have changed the conclusions of this study. Also, the difference between the Netherlands and Belgium may, at least partly, be explained by the difference in responding hospitals : 44% versus 86% teaching hospitals.

Not many survey studies have been performed for PJI diagnosis and treatment. A survey on PJI treatment, sent to microbiologists, showed consensus on duration of postoperative antibiotic treatment (at least 4 weeks), but the antibiotic free period after that remained a point of discussion (*9*). Anagnostakos and Kohn performed a study on diagnosis and treatment of hip PJI in 2011, and Holl did the same on hip and knee PJI. Both written in German, their main conclusions were that the way to perform diagnosis and treatment differs between hospitals, and more guidance would be desirable (*3,8*).

Many factors in PJI diagnosis and treatment remain unclear, and many differences are seen between hospitals and between countries. Recently, guidelines have been published, but these are not (yet) followed accurately. On other questions, such as empirical antibiotic use, local antibiotics, use of spacers and the period before reimplantation should be considered, the guidelines do not give answers.

The variety between respondents indicates that more guidance is needed. Perhaps, nationally or locally adapted guidelines might be followed more directly. Standardized diagnosis and treatment options could result in an easier way to compare the outcome of different hospitals and diagnosis and treatment methods. This may result in better understanding how to treat patients with PJI and may decrease health care costs when a clear, evidence based treatment protocol is used by all hospitals. Further research is definitely needed to answer most questions.

Contribution of authors

All authors conceived and designed the study. JK analyzed the data. JK and SC wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

Previous presentations

This manuscript has been orally presented at the annual congress of the European Bone and Joint Infection Society (EBJIS), in Utrecht, the Netherlands on September 11th 2014.

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