Le Infezioni in Medicina, n. 3, 141-150, 2009

Lavori originali

Original articles

Combined Diagnostic Tool for joint prosthesis infections

Combined Diagnostic Tool per le infezioni di protesi articolari

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INTRODUCTION

Joint prosthesis is a common and successful procedure with more than 800,000 implants per year in the United States of America. Joint prosthesis infection is a potentially devastating and expensive complication and it has been shown to develop after up to 2% of uncomplicated arthroplasties, while studies have reported an incidence as high as 12.4% in certain patient populations [1-5].

Distinguish joint arthroplasties with infection from those without still presents a diagnostic challenge, as none of the tests commonly used to diagnose infection appear to be 100% sensitive or specific when applied to patients who have had a joint prosthesis.

The acute infection usually shows, in fact, some characteristic clinical and laboratory features, whereas the diagnosis of the relatively frequent subacute or low grade chronic infections is much more problematic. Clinical examinations, laboratory studies, radiographs, nuclear scans, joint aspirations and histological frozen section analysis all have notable rates of false positive and false negative results [6-10].

Misdiagnosis of joint prosthesis infection may delay proper intervention or may lead to inappropriate treatment. Aseptic prosthetic loosening may in fact be treated with one stage revision operation, while infection is the most feared complication of total joint surgery as it threatens the function of the joint, limb preservation and occasionally even the life of the patient, requiring a suitable and much more complex medico-surgical treatment [11].

To reduce the risk of misdiagnosis, in the clinical setting multiple different diagnostic tests are then usually performed in a staged process and the final diagnosis comes from their combined evaluation.

While more and more sophisticated (and expensive) diagnostic procedures are proposed to make more reliable the diagnosis of septic complication in joint prosthesis, the choice and the evaluation of the various tests to be performed in a given patient still depends largely on a subjective evaluation process of the physician and on logistical and/or cost restrictions of different centers.

The aim of this study is to propose and prospectively evaluate the efficacy of a new automatic calculation tool of multiple independent diagnostic tests, compared to the "gold" standard of the intra-operative tests, in an effort to provide an objective and reproducible instrument for the evaluation of the overall and relative contribution of each exam to the final diagnostic output. While the proposed calculation tool, for the purpose of this study, has been applied to the differential diagnosis of painful joint prosthesis, it appears potentially useful in other clinical conditions that require multiple combined independent diagnostic testing.

METHODS

"Combined Diagnostic Tool" rationale

When we perform a series of independent tests in a given subject in the suspect of a given disease, we may observe some positive and some other negative tests. What is the respective contribution of positive and negative tests to the final diagnostic output and, in case of conflicting results, how do we compare positive and nega-

tive results? Specificity of a test measures the proportion of True Negatives (TN) and False Positives (FP), according to the formula: TN/(TN+FP). A test with a specificity of 0.8 will be able to correctly exclude the disease in 80% of the subjects (TN), while the remaining 20% will be FP. Sensitivity measures the proportion of actual positives which are correctly identified as such (True Positives, TP) and the number of False Negatives (FN). Sensitivity is in fact expressed by the formula: TP/(TP+FN). If a given test has a sensitivity of 0.7, it will correctly detect the disease in 70% of the patients (TP) and it will not in the remaining 30% (FN). In a given subject, a positive or negative test, will have, respectively, the following chances of being:
TN = specificity of the negative test
FN = 1 - sensitivity of the negative test
TP = sensitivity of the positive test
FP = 1 - specificity of the positive test
Consider a test with a specificity and sensitivity of, respectively, 0.8 and 0.7. If that test is negative in a subject, he will have 80% (specificity of the negative test) chance of being a TN and 30% (1 - sensitivity of the negative test) of being a FN.
The relative proportion of TN and FN of a negative test, will be called Negative Test Index (NTI), and is calculated according to the formula:

NTI = TN/FN = specificity of the negative test/1 - sensitivity of the negative test

NTI indicates the relative chances that the subject, seen as negative by a given test, has to be TN compared to FN. The higher the value of NTI, the higher the chance that test correctly indicated that subject as NOT having the disease. In the example: NTI = TN/FN = 80/30 = 2.66. The chance that this negative test correctly indicated the subject as NOT infected is 2.66 times the chances that it gave a falsely negative result.
Following the example, if the same test is positive in a subject, he will have 70% (sensitivity of the positive test) chance of being a TP and 20% (1 - specificity of the positive test) of being a FP. The ratio between the chance of being a TP and that of being a FP will be called in this study Positive Test Index (PTI):

PTI = TP/FP = sensitivity of the positive test/1 - specificity of the positive test

PTI indicates the relative chance that the subject is a TP compared to a FP. The higher the value of PTI, the higher the chance that test correctly indicated that subject as HAVING the disease. In the example: PTI = TP/FP = 70/20 = 3.50. The chance that this positive test correctly indicated the subject as INFECTED is 3.50 times the chances that it gave a falsely positive result.
If we have n independent tests, performed on a same subject, the combined chance of positive or negative results to be true is, respectively, the following:

$$PTI^n = TP^a * TP^b * TP^n / FP^a * FP^b * FP^n =$$
$$NTI^n = TN^a * TN^b * TN^n / FN^a * FN^b * FN^n =$$

The ratio between PTI and NTI will be indicated as the Combined Tests Index (CTI):

$$CTI = PTI^n / NTI^n$$

CTI expresses how many times the output of the combined positive tests is, compared to the output of the combined negative tests. The higher its value, the higher the chance the positive results are "more true" and that the subject HAS the disease and viceversa.
The "Combined Diagnostic Tool" (CDT), for diagnosing septic complications in joint prosthesis, is a software in which the reference values of sensitivity and specificity of the most common diagnostic tests of infection of joint prosthesis have been implemented. Based on these reference values and on the results of different tests in a given subject, the software is able to automatically calculate the NTI, PTI and CTI of that subject (Table 1). Values of CTI >1 are in favor of infection. Values of CTI <1 are in favor of an aseptic painful prosthesis. The software also allows to assess the relative contribution of any additional test and, in this way, it permits to objectively evaluate the relative cost/benefit of any additional diagnostic procedure.

Bibliographic research

For the Combined Diagnostic Tool to work properly in the clinical setting, it is mandatory to accurately define the respective sensitivity and specificity of each diagnostic test that is included in the diagnostic process for a given disease. To this aim, Medline and Embase research of published papers from 1990 to 2008, concerning the relative efficacy of different diagnostic procedures commonly used for differential diagnosis of painful joint prosthesis has been performed. When more values of sensitivity or specificity for a given test were available, their mean value has been used for the Combined Diagnostic Tool.

Clinical application

The Combined Diagnostic Tool has been

Table 1 - Combined Diagnostic Tool (CDT) software. In the example below: Positive Tests Index (PTI) = 35.55. Combined positive tests have 35.55 chance of seeing the subject under study as a True Positive (TP), compared to 1 chance that he/she is a False Positive (FP); Negative Tests Index (NTI) = 4050. Negative tests have 4050 chances of seeing the subject under study as a True Negative (TN), compared to 1 chance that he/she is a False Negative (FN); the Combined tests Index (CTI) is then 0.008, or the relative chances that the subject has an infected prosthesis are 8:1000. The subject is to be considered not infected.

		Test A	*Test B*	*Test C*	*Test N*		
Positive tests	TP (sensitivity of the positive test)/ FP (1 - specificity of the positive test)	0.91 / 0.14	0.93 / 0.17			PTI	35.55
						CTI	0.0087
Negative tests	TN (specificity of the negative test)/ FN (1 - sensitivity of the negative test)		0.81 / 0.18	0.9 / 0.001		NTI	4050.0

prospectively evaluated in a consecutive series of 36 patients, affected by a painful joint prosthesis, that presented to our observation in years 2007-2008.

Each patient underwent multiple diagnostic tests to exclude or confirm the suspect of infection. The choice of the diagnostic tests was based on the diagnostic process currently in use at our institution. This include first line tests: clinical examination, laboratory testing (erythro-sedimentation rate, ESR, C-reactive protein, CRP) and plain x-ray examination; then a choice of second line tests: sonography, joint aspiration (cultural examination and white cell blood count, WBC), 99Technetium bone scan; in selected cases third line tests were performed: leucocyte bone scan, positron emission tomography (PET), computer tomography (CT) scan.

Pre-operative tests results were collected by a dedicated investigator, to assess the NTI, PTI and CTI of each patient with the Combined Diagnostic Tool. Based on these pre-operative tests and, in selected cases, on the additional testing of intra-operative frozen sections, all the patients underwent surgical intervention and one- or two-stage revision of the prosthesis.

At intervention, histological and cultural examinations were performed from two independent investigators, not aware of the results of the Combined Diagnostic Tool. The results of the intra-operative tests were then compared to the output of pre-operative tests, using the Combined Diagnostic Tool. Intra-operative cultural sampling was performed as it follows. At least three periprosthetic samples from different sites were submitted to the laboratory for culture. Liquid samples that were aspirated from the operative site with use of a sterile syringe were immediately inoculated into Bactec 9000 Blood Culture Systems (Becton Dickinson Diagnostic Instruments, Sparks, Maryland) and were incubated for seven days. Positive flasks were subcultured in aerobic and anaerobic agar media. Swab samples were obtained by passing a sterile swab over the area of tissue, bone, or fluid that was suspected of being infected. Solid tissue samples from pseudocapsule, the membrane around the prosthesis or tissue that was suspected to be infected were immediately placed into a separate sterile universal bottle. Solid tissue samples and swab samples were cultured in aerobic and anaerobic agar media and in thioglycolate broth enriched with vitamin K and hemin and were incubated for ten days. Positive cultures were sent for organism identification and sensitivity testing.

Samples for frozen-section analysis and permanent histological analysis were obtained from the pseudocapsule, the membrane around the prosthesis, or tissue that was suspected to be infected. Each of two samples from each patient were divided into two parts, one for frozen-section analysis and one for permanent paraffin-embedded section analysis. The samples that were used for frozen-section analysis were snap-frozen in carbon dioxide; 4- m sections were then cut and stained with hematoxylin and eosin. The samples used for histological analysis of paraffin-embedded sections were fixed in formalin and embedded in paraffin prior to staining with hematoxylin and eosin. The most cellular areas in the tissue sample were chosen for evaluation, and the number of neutrophils (in the frozen and paraffin-embedded sections), lymphocytes, and plasma cells (in the paraffin-embedded sections) per high-power field (×400) in at least ten separate microscopic fields were counted. The histological Feldman criterion, defined as the presence of at least five neutrophils per high-power field (×400) in at least five sepa-

rate microscopic fields was used [9, 12, 13].
For comparison purposes, pre-surgical tests outcome, obtained by means of the Combined Diagnostic Tool, has been compared to intra-operative results. A patient was considered to be infected if either one of the following conditions applied:

- positive intra-operative cultural examination;
- positive permanent histological finding.

The present study was considered double-blinded in the sense that the results of pre-operative tests, used to perform calculations with the Combined Diagnostic Tool, were collected by one of the investigator before the intra-oper-

Table 2 - Reference values of sensitivity, specificity used in the Combined Diagnostic Tool (bibliographic references in brackets).

Test		*Reference values used for calculations*
	Sensitivity	0,84
C-reactive Protein [2, 14-17]	Specificity	0,87
	Sensitivity	0,78
Erythrosedimentation rate [2, 6, 15]	Specificity	0,78
	Sensitivity	0,98
Serum interleukin-6 [14, 18]	Specificity	0,91
	Sensitivity	0,33
Procalcitonin [14]	Specificity	0,98
	Sensitivity	0,43
TNF-alpha [14]	Specificity	0,94
	Sensitivity	0,29
White-blood cell count [17, 19]	Specificity	0,94
	Sensitivity	0,79
Plain X-ray [20, 21]	Specificity	0,55
	Sensitivity	0,75
Helical CT (Bone) [21]	Specificity	0,30
	Sensitivity	1,00
Helical CT (Soft Tissues) [21]	Specificity	0,87
	Sensitivity	1,00
Sonography [22]	Specificity	0,77
	Sensitivity	0,69
Three Phase Bone scan [6, 20, 23]	Specificity	0,83
	Sensitivity	0,62
Leukocite Bone scan [17, 24]	Specificity	0,88
	Sensitivity	0,85
FDG-PET [25]	Specificity	0,93
	Sensitivity	0,28
Pyrexia (5 days post-op) [26]	Specificity	0,62
	Sensitivity	0,97
Histology [16, 19]	Specificity	0,96
	Sensitivity	0,45
Histology (frozen section) [2, 27, 28]	Specificity	0,96
	Sensitivity	0,86
Intra-operative coltures [2, 19]	Specificity	0,95
	Sensitivity	0,69
Joint aspiration (coltural examination) [2, 6, 16, 17, 19, 29, 30]	Specificity	0,84
	Sensitivity	0,33
Joint aspiration (white blood cell) [2]	Specificity	0,99
	Sensitivity	0,89
Joint aspiration (Neutrophils >80%) [2]	Specificity	0,85

ative results were given and the investigators that performed the intra-operative histological and cultural examinations were not aware of pre-operative results.
Statistical analysis has been performed with the unpaired Student's t test. The level of significance was set at $p<0.05$.

RESULTS

Data regarding respective sensitivity and specificity of different diagnostic tests, used in the Combined Diagnostic Tool, are summarized in Table 2. The literature review confirms the lack of a single test that is 100% specific and

Table 3 - Data from patients with final diagnosis of septic joint prosthesis (N=21).

	Final diagnosis	Time from implant (years)	C-reactive protein	Erythrosedimentation rate	White-blood cell count	Sonography	Helical CT** (Soft Tissues)	Plain X-ray	Helical CT (Bone)	Three Phase Bone scan	Leukocite Bone scan	FDG-PET***	Histology (frozen section)	Joint aspiration (cultural examination)	Joint aspiration (WBC****)	Neutrophil count >80%	Positive Tests Index (PTI)	Negative Tests Index (NTI)	Combined Tests Index (CTI)
	S THR	0,2	-	+	-	+									+		63,876	7,235	8,829
	S THR	2,0	-	+	-			-		+	+			-	+	+	13275,97	49,84	266,388
	S THR	2,0	+	+	+			-									99,48	2,54	39,243
	S THR	3,0	+	+	-						+			+			465,73	1,32	353,630
	S THR	1,0	+	+	-			-			+			-	+	-	173311,23	5397,63	32,109
	S THR	1,0	+	+	+	-		-	-	-			+	-	+	+	217182,14	1674,38	129,709
	S THR	1,5	+	-	-	+	+	-	-	-	+			+			4367,38	37,68	115,907
	S THR	1,0	+	+	-	+		-			-				+	+	18791,00	7,59	2476,737
	S THR	1,5	+	+	-			-		-		+	+	-	-	-	3018,89	272,47	11,080
	S THR	3,0	+	+	-			+					+	+			1820,97	1,32	1382,667
	S THR	3,0	-	+	-	+		-		-	+			+			10370,59	48,24	214,970
	S TKR	2,5	+	-	-			-		-	+			-	+	+	6144,92	130,32	47,154
	S TKR	0,6	+	-	-			-		+				+	+	+	20904,71	11,94	1751,253
	S TKR	1,0	+	-	-			-		+	+			-	+	+	24226,51	32,44	746,787
	S TKR	1,0	+	+	-			-						+	+	+	18534,59	3,34	5552,605
	S TKR	1,0	+	+	-			-		+							87,908	3,34	26,336
	S TKR	4,0	+	+	-	+		-		+	+		+	+	-	-	248602,86	2934,87	84,707
	S TKR	4,0	+	+	+			-						-	+		3282,85	6,89	476,534
	S TKR	2,0	-	+	+			+		+	+			-	+		17223,07	14,93	1153,665
	S TKR	6,0	+	+	-			-		-			+				248,61	8,78	28,315
	S TER	6,0	+	-	-			+		+				-			151,67	3,58	42,376
Performed tests		21	21	21	6	1	19	2	13	9	1	5	17	12	10				
% Positive Tests		0,81	0,76	0,19	0,83	1,00	0,16	0,00	0,54	0,90	1,00	1,00	0,47	0,83	0,70				
MEAN		2.0															37246,43	507,17	711,48
SD		2.0															74918,75	1327,57	1298,42

*S THR - S TKR - S TER: respectively, septic total hip, knee and elbow replacement. **CT: computed tomography. ***FDG - PET: Fluorodeoxyglucose-Positron Emission Tomography. ****WBC: White cells count

sensitive for diagnosing joint prosthesis infection. Most of the good quality retrieved papers regard laboratory tests [2, 6, 14-19] and imaging techniques [6, 17, 20-25] even if data concerning traditional radiological exams (plain x-ray and sonography) look remarkably poor and from limited series of patients.
We also could not find any published data on sensitivity and specificity of clinical signs and symptoms (only one study [26] concerns the occurrence of pyrexia in the immediate post-operative period).
The remaining good quality studies are focused on invasive procedures like joint aspiration [2, 6, 16, 17, 19, 29, 30], histology [2, 27, 28] and intra-operative coltures [2, 19]. Other important limitations, regarding the reliability of reference values of diagnostic tests, that emerge from the present review of the literature, are reported in the Discussion chapter. Analytical results from pre-operative diagnostic test from the 36 patients are reported in Tables 3 and 4.
21 patients were diagnosed as affected by a septic joint prosthesis on the basis of intra-operative findings (intra-operative cultural and/or permanent histological findings): 11 septic total hip prosthesis, 9 septic total knee prosthesis, 1 septic elbow prosthesis. The remaining 15 patients were diagnosed on the same basis, to have an

Table 4 - Data from patients with final diagnosis of aseptic joint prosthesis (N=15).

	Final diagnosis	*Time from implant (years)*	*C-reactive protein*	*Erythrosedimentation rate*	*White-blood cell count*	*Sonography*	*Helical CT** (Soft Tissues)*	*Plain X-ray*	*Helical CT (Bone)*	*Three Phase Bone scan*	*Leukocite Bone scan*	*FDG-PET****	*Histology (frozen section)*	*Joint aspiration (cultural examination)*	*Joint aspiration (WBC****)*	*Neutrophil count >80%*	*Positive Tests Index (PTI)*	*Negative Tests Index (NTI)*	*Combined Tests Index (CTI)*
	A THR	2,0	-	+	-			-	-	+	+		-	-	-		67,80	239,97	0,283
	A THR	3,0	-	-	-	+		-		+		+	-	-	-		52,27	1204,14	0,043
	A THR	4,0	-	+	-	-	-	+	+	+	-		-				25,475	191465,145	0,00013
	A THR	1,5	+	+	-			-		+	-				+		454,78	3837,42	0,119
	A THR	4,0	+	+	-	-	-	+	+	+	-		-				162,50	34851,95	0,005
	A THR	5,0	-	+	-	+		-		-	-						15,05	109,64	0,137
	A THR	4,5	-	+	-	-	+	+		+	+		-	-	-	-	890,848	30045,852	0,030
	A THR	1,0	-	-	-	-		-		+	+						19,397	5049,713	0,004
	A THR	4,0	-	-	+	-		+		-	-						7,697	9043,84	0,001
	A THR	1,5	-	+	-	-		-		-	+		-				17,198	6457,012	0,003
	A TKR	6,0	-	-	-			+		+		+		-	-	-	82,595	802,748	0,103
	A TKR	1,0	-	+	-			+						-	-	-	3,50	569,03	0,006
	A TKR	2,0	-	-	+			-		+	-			-	-	-	17,59	3511,81	0,005
	A TKR	3,0	+	-	-			+		+				-	-	-	43,388	146,122	0,297
	A TKR	2,0	+	-	-			-		-				-			6,38	85,34	0,075
Performed tests		15	15	15	8	3	15	3	14	10	2	6	8	7	5				
% Negative Tests		0,73	0,47	0,87	0,75	0,67	0,53	0,33	0,29	0,60	0,00	1,00	1,00	0,86	1,00				
MEAN		2.9															124,431	19161,315	0,074
SD		1.5															240,921	48878,517	0,099

*A THR - A TKR: respectively, aseptic hip and knee replacement. **CT: computed tomography. ***FDG - PET: Fluorodeoxyglucose-Positron Emission Tomography. ****WBC: White cells count.

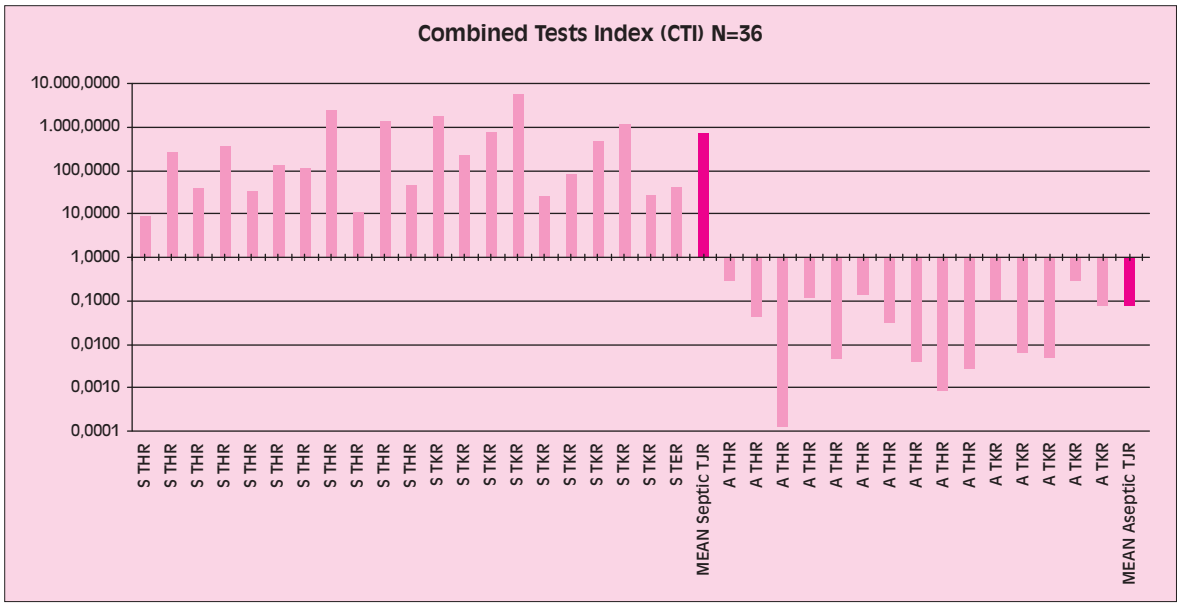

Figure 1 - (Note that y axis is in logarithmic scale) Combined Tests Index (N=36). (S THR - S TKR - S TER: respectively, septic total hip, knee and elbow replacement; A THR - A TKR: respectively, aseptic hip and knee replacement; TJR: total joint replacement). Mean values are statistically different (p=0.04).

aseptic loosened of painful hip (10 cases) or knee prosthesis (5 patients). Male/female, age and time from prosthetic implant were: 8/13, 59±10 and 2.0±2.1, for infected cases and 4/11, 63±8 and 2.9±1.5 for not infected cases.

All of the infected patients had a CTI >1 (range: from 8.8 to 5552.6), while all of the 15 patients who had negative intra-operative results for infection, had a CTI <1 (range: from 0.00013 to 0.297) (Figure 1).

Overall Positive Tests Index was higher in infected cases (37246±74918) compared to non infected prosthesis (124±240), but not quite statistically significant (p=0.06). In a reverse manner, Negative Tests Index was higher in non infected patients compared to infected cases (19161±48878 versus 507±1327), but the difference was still not statistically significant (p=0.08). In non infected prosthesis, the NTI was lower than PTI (124±240 versus 1916±48878), but the difference was not statistically significant (p=0.14).

These values probably reflect the high standard deviations, due to the heterogeneous series of tests performed in each case and the relatively limited number of patients included in the study.

On the contrary, in infected prosthesis, the PTI was shown to be significantly higher than NTI (p=0.03) (37246±74918 versus 507±1327) and the Combined Tests Index showed a significant (p=0.04) difference between the two groups of patients: 711.48±1298.42 in infected, compared to 0.074+-0.099 in non-infected cases.

DISCUSSION

In failed arthroplasties the distinction between aseptic loosening and infection is important for the prognosis and the choice of surgical and medical management. Misdiagnosis may in fact lead to delayed of wrong treatment.

Bibliographic research points out the lack a 100% sensitivity and specificity of a single test for differential diagnosis between aseptic and septic painful or loosened prosthesis and provides the basis for the currently used clinical approach of multiple diagnostic testing. It also shows the following main limitations of an effort to provide a single fixed value of sensitivity and specificity of a given test to diagnose joint prosthesis infection:

- there is an objective lack of high quality papers, especially for traditional radiology and for physical examination. We tried, whenever possible, to refer to high-level meta-analysis or to prospective evidence-based level I papers to find the most reliable data, but our findings show that some of the most current-

ly used diagnostic tests (e.g. sonography) are probably not adequately studied and available data are based on isolated studies on limited series of patients.
- Reference normal values of a given diagnostic test may differ among Authors.
- Populations studied for validation of the same or different tests may vary in different studies.
- Inter-observer variability and different diagnostic criteria are a possible source of bias, especially for imaging techniques and histological examination.
- When more than one study is found, sensitivity and specificity values for a same test may vary among different Authors. When this occurred (e.g. for C-reactive protein values), for the purpose of this study the mean value of the sensitivities and specificities reported by the different studies has been calculated and used as a reference value for the Combined Diagnostic Tool; the reader should be aware that this procedure may introduce a bias, since not necessarily all studies are perfectly comparable. However the other option, to choose one single study as reference, may also appear not adequate to correctly represent the overall experience of different centers.
- Some studies may not have been retrieved in the present analysis.

It should be pointed out that all the above mentioned limitations do also apply every time we interpret the diagnostic findings in a given patient, on a subjective basis. This limits appear, in fact, intrinsic to our current scientific knowledge in the field, even if in a more empiric diagnostic process they are not always clearly quantified.

For this reason, in our opinion, these limitations do not prevent the use of a calculation tool like that proposed, once the bibliographic sources and limits of research have been made clear to the possible user.

In should also be noted that bibliographic research of reference values is a work-in-progress and the Combined Diagnostic Tool is thought may be periodically updated according to any relevant new literature data.

In this study, intra-operative findings have been considered as the golden standard in the diagnosis of infected prosthesis, but it is worth noting that both intra-operative cultural examination and histological findings are prone to errors. As we may observe in Table 2, histology has been reported to have a sensitivity of 1 or 0.94 and a specificity of 0.98 and 0.94, while intra-operative cultural examination values range from 0.78 to 0.94 for sensitivity and from 0.92 to 0.97 for specificity.

Should we apply the Combined Diagnostic Tool to this tests, we would see that intra-operative cultural examination and histology, when positive in a subject, have a Positive Test Index of, respectively, 17.2 and 24.2, when used alone and a remarkable Positive Tests Index of 417, when combined.

In other words, if in a patient both of these tests are found positive, he/she will have 417 chance versus 1 that that positive results are true and that he/she is really infected.

For comparison, the combination of C-reactive protein and erythrosedimentation rate, considered one of the most powerful diagnostic combination of prosthetic infections [2], has a PTI of "only" 22.9.

The main drawback of intra-operative findings (except frozen sections) is that they provide the required answer only days after the surgical intervention, when the decision on the treatment had been already necessarily done. The Combined Diagnostic Tool, instead, appears to provide a pre-operative assessment of the risk of infection that is comparable to that obtained with the intra-operative findings, but that it may be used in the pre-operative decision making process.

It also allow to quantify the relative contribution of each diagnostic test to the final diagnostic output and this could be used for simulation and to estimate the relative cost to benefit ratio of different diagnostic procedures.

Validation of the Combined Diagnostic Tool in a larger series of patients in this and in other challenging diagnostic clinical settings and collection of data regarding the cost/benefit values of diagnostic tests is the object of currently ongoing research.

Source of funding

The present research is part of a Current Research Project of the Istituto Galeazzi I.R.C.C.S. of Milano, Italy, financed by the Italian Ministry of Health. The funding source did not play a role in the investigation and no direct financial support has been or will be received by the any of the investigators for the study.

Key words: diagnosis, infection, hip prosthesis, knee prosthesis, joint prosthesis

SUMMARY

While diagnosing infection of a joint prosthesis often requires a multi-modal approach, evaluation of combined multiple diagnostics is still a rather subjective process. Based on the known sensitivity and specificity of commonly performed tests for joint prosthesis infection, we developed the Combined Diagnostic Tool, a software program that automatically allows the Combined Tests Index (CTI) to be calculated. The CTI indicates, in a given subject, the relative probability of a combined series of positive tests being true compared to negative tests. CTI values above 1 indicate a progressively higher chance of a prosthesis being infected and vice versa. Double-blind, prospective evaluation of CTI, compared to intra-operative cultural and histological findings, was performed in a consecutive cohort of 36 patients. 21 patients had positive intra-operative findings for infection. All of them had a pre-operative CTI >1 (range: 8.8 to 5552.6; mean: 711±1298). 15 patients had negative intra-operative results. All had a CTI <1 (range: 0.00013-0.297; mean 0.074±0.099). The difference in CTI between the two groups was statistically significant (p=0.04). Our results show that the Combined Tests Index may be a useful indicator for differential diagnosis of prosthetic infection.

RIASSUNTO

Mentre la diagnosi di infezione nelle protesi articolari richiede spesso un approccio multi-modale, la valutazione di tests diagnostici combinati è ancora un processo soggettivo. Utilizzando i dati di sensibilità e specificità dei tests diagnostici comunemente eseguiti per la diagnosi di infezione protesica, abbiamo sviluppato il Combined Diagnostic Tool, un programma che calcola automaticamente il Combined Tests Index (CTI); il CTI indica, nel singolo soggetto, le possibilità di essere vera di una combinazione di tests diagnostici positivi, comparati con i tests negativi. Un CTI >1 indica una possibilità progressivamente maggiore di una protesi di essere infetta e viceversa.

L'indice CTI è stato valutato in uno studio prospettico, in doppio cieco, in comparazione con l'esame colturale ed istologico intra-operatorio, in una coorte consecutiva di 36 pazienti. Ventuno pazienti avevano dati intra-operatori positivi per infezione. In tutti questi casi, si è osservato un CTI >1 (minimo: 8,8; massimo 5552,6; media: 711±1298). Quindici pazienti avevano dati intra-operatori negativi. Tutti questi pazienti hanno mostrato un CTI <1 (0,00013-0,297; media 0,074±0,099). La differenza di CTI nei due gruppi era statisticamente significativa (p=0,04).
Il Combined Tests Index appare utile nella diagnosi differenziale di infezione di protesi articolari.

REFERENCES

[1] Jacofsky J.J., Campbell M.D. The infected total knee arthroplasty part 1: identification and diagnosis in the primary care setting. *Hospital Physician* 29-32, 2006.
[2] Spangehl M.J., Masri B.A., O'Connell J.X., Duncan C.P. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *J. Bone Joint Surg. Am*. 81, 72-83, 1999.
[3] Hanssen A.D., Rand J.A. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. *Instr. Course Lect*. 48, 111-122, 1999.
[4] Sculco T.P. The economic impact of infected total joint arthroplasty. *Instr. Course Lect.* 42, 349-351, 1993.
[5] Grogan T.J., Dorey F., Rollins J., Amstutz H.C. Deep sepsis following total knee arthroplasty. Ten-year experience at the University of California at Los Angeles Medical Center. *J. Bone Joint Surg. Am.* 68, 226-234, 1986.
[6] Levitsky K.A., Hozack W.J., Balderson R.A., et al. Evaluation of the painful prosthetic joint. Relative value of bone scan, sedimentation rate, and joint aspiration. *J. Arthroplasty* 6, 237-244, 1991.
[7] Athanasou N.A., Pandey R., deSteiger R., Crook D., Mclardy Smith P. Diagnosis of infected frozen section during revision arthroplasty. *J. Bone Joint Surg.* 77B, 28-33, 1995.
[8] Kraemer W.J., Saplys R., Waddell J.P., Morton J. Bone scans, gallium scans and hip aspiration in the diagnosis of infected total hip arthroplasty. *J. Arthroplasty* 8, 611-615, 1993.
[9] Lonner J.H., Desai P., Dicesare P.E., Steiner G., Zuckerman J.D. The reliability of analysis of intraoperative frozen sections for identifying active infection during revision hip or knee arthroplasty. *J. Bone Joint Surg.* 78A, 1553-1558, 1996.
[10] Duff G.P., Lachiewicz P.F., Kelley S.S. Aspiration of the knee joint before revision arthroplasty. *Clin. Orthop.* 331, 132-139, 1996.
[11] Lonner J.H., Beck T.D., Rees H., Roullet M.,

Lotke P.A. Results of two-stage revision of the infected total knee arthroplasty. *Am. J. Knee Surg.* 14 (1), 65-67, 2001.
[12] Feldman D.S., Lonner J.H., Desai P., Zuckerman J.D. The role of intraoperative frozen sections in revision total joint arthroplasty. *J. Bone Joint Surg. Am*. 77, 1807-1813, 1995.
[13] Athanasou N.A., Pandey R., de Steiger R., McLardy Smith P. The role of intraoperative frozen sections in revision total joint arthroplasty. *J. Bone Joint Surg. Am*. 79, 1433-1434, 1997.
[14] Bottner F., Wegner A., Winkelmann W., Becker K., Erren M., Götze C. Interleukin-6, procalcitonin and TNF-alpha: markers of peri-prosthetic infection following total joint replacement. *J. Bone Joint Surg. Br.* 89 (1), 94-99, 2007.
[15] Greidanus N.V., Masri B.A., Garbuz D.S., et al. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. *J. Bone Joint Surg. Am*. 89 (7), 1409-1416, 2007.
[16] Fink B., Makowiak C., Fuerst M., Berger I., Schäfer P., Frommelt L. The value of synovial biopsy, joint aspiration and C-reactive protein in the diagnosis of late peri-prosthetic infection of total knee replacements. *J. Bone Joint Surg.* 90 (7), 874-878, 2008.
[17] Virolainen P., Lähteenmäki H., Hiltunen A., Sipola E., Meurman O., Nelimarkka O. The reliability of diagnosis of infection during revision arthroplasties. *Scand. J. Surg.* 91, 178-181, 2002.
[18] Di Cesare P.E., Chang E., Preston C.F., Liu C.J. Serum interleukin-6 as a marker of periprosthetic infection following total hip and knee arthroplasty. *J. Bone Joint Surg. Am*. 87 (9), 1921-1927, 2005.
[19] Müller M., Morawietz L., Hasart O., Strube P., Perka C., Tohtz S. Diagnosis of periprosthetic infection following total hip arthroplasty - evaluation of the diagnostic values of pre- and intraoperative parameters and the associated strategy to preoperatively select patients with a high probability of joint infection. *J. Orthop. Surg*. 3, 31-35, 2008.
[20] Temmerman O.P., Raijmakers P.G., Berkhof J., Hoekstra O.S., Teule G.J., Heyligers I.C. Accuracy of diagnostic imaging techniques in the diagnosis of aseptic loosening of the femoral component of a hip prosthesis: a meta-analysis. *J. Bone Joint Surg. Br*. 87 (6), 781-785, 2005.
[21] Cyteval C., Hamm V., Sarrabere M.P., Lopez F.M., Maury P., Taourel P. Painful Infection at the Site of Hip Prosthesis: CT Imaging. *Radiology* 224 (2), 477-483, 2002.
[22] van Holsbeeck M.T., EyIen W.R., Sherman L.S., et al. Detection of Infection in Loosened Hip Prostheses: Efficacy of Sonography. *Am. J. Roentgenol*. 163, 381-384, 1994.
[23] Nagoya S., Kaya M., Sasaki M., Tateda K., Yamashita T. Diagnosis of peri-prosthetic infection at the hip using triple-phase bone scintigraphy. *J. Bone Joint Surg. Br.* 90 (2), 140-144, 2008.
[24] Pakos E.E., Trikalinos T.A., Fotopoulos A.D., Ioannidis J.P. Prosthesis infection: diagnosis after total joint arthroplasty with antigranulocyte scintigraphy with 99mTc-labeled monoclonal antibodies - a meta-analysis *Radiology* 242 (1), 101-108, 2007.
[25] Chryssikos T., Parvizi J., Ghanem E., Newberg A., Zhuang H., Alavi A. FDG-PET imaging can diagnose periprosthetic infection of the hip. *Clin. Orthop. Relat. Res*. 466 (6), 1338-1342, 2008.
[26] Ghosh S., Charity R.M., Haidar S.G., Singh B.K. Pyrexia following total knee replacement. *Knee* 13 (4), 324-327, 2006.
[27] Kanner W.A., Saleh K.J., Frierson H.F. Jr. Reassessment of the usefulness of frozen section analysis for hip and knee joint revisions. *Am. J. Clin. Pathol*. 130 (3), 363-368, 2008.
[28] Bori G., Soriano A., García S., Mallofré C., Riba J., Mensa J. Usefulness of histological analysis for predicting the presence of arthroplasty for the treatment of infection microorganisms at the time of reimplantation after hip resection. *J. Bone Joint Surg.* 89, 1232-1237, 2007.
[29] Van den Bekerom M.P., Stuyck J. The value of pre-operative aspiration in the diagnosis of an infected prosthetic knee: a retrospective study and review of literature. *Acta Orthop. Belg*. 72 (4), 441-447, 2006.
[30] Gallo J., Kolar M., Dendis M., et al. Culture and PCR analysis of joint fluid in the diagnosis of prosthetic joint infection. *New Microbiol.* 31 (1), 97-104, 2008.