Alpha defensin: a diagnostic accuracy depending on the infection definition used.

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SUMMARY

Background: The purpose of this study was to evaluate the Alpha Defensin qualitative detection (ADLF) sensitivity and specificity as compared to three standard classifications in the diagnostic management of chronic prosthetic joint infections (PJI).

Materials and methods: A multicenter cohort of 136 patients with a painful arthroplasty was classified into either infected or non-infected according to the Musculoskeletal Infection Society (MSIS) score, Infectious Diseases Society of America (IDSA) score, European Bone and Joint Infection Society (EBJIS) score. The sensitivity and specificity of the ADLF test were calculated for each score. Spearman's correlations between all scores were then analyzed, and multiple logistic regression was applied to identify independent variables strongly connected to the PJI probability.

Results: The EBJIS score was positive in 68 patients, IDSA score in 50 patients, MSIS score in 41 patients, and ADLF in 40 patients. The ADLF sensitivity was 87.8% compared to MSIS, 70% compared to IDSA, and 55.8% compared to EBJIS. The ADLF specificity was in the range of 94%–97%. A good correlation was observed between synovial fluid cultures and ADLF (r=0.73). Low to excellent correlations were recorded between ADLF and the EBJIS (r=0.58), IDSA (r=0.68), and MSIS (r=0.84) scores. The synovial fluid's white blood cell count was proven to be the biological test that most influenced the probability of a positive culture (p value: 0.005).

Discussion: The ADLF sensitivity was variable, whereas its specificity was excellent. The EBJIS score results significantly differed from those obtained via cultures, which possibly explains the ADLF low sensitivity compared to that of the EBJIS score.

Key words : prosthetic joint infection, alpha defensin, synovial fluid, white blood cell count, scores

INTRODUCTION

Although prosthetic joint infection (PJI) is a rare event, it represents a severe complication and is associated with high morbidity, the need for complex treatments, and substantial healthcare costs.[1] In addition to prolonged hospitalization, it can be associated with unsatisfactory functional results or even permanent disability, such as arthrodesis or leg amputation.[2] Therefore, the preoperative PJI diagnosis proves to be critical for optimal surgical and antimicrobial treatments.[3]

The 2011 introduction of the MusculoSkeletal Infection Society (MSIS) criteria for PJIs, which were later modified in 2013 and 2018 by the International Consensus Meeting (ICM),[4] resulted in improved diagnostic confidence.[5,6] These criteria enable the PJI diagnosis through scores pertaining to clinical observations, laboratory tests, and tissue histology.[7] Although these criteria are often considered as the gold standard of PJI diagnosis,[8] synovial fluid biomarkers (interleukin-6, leukocyte esterase, and alpha-defensin) are increasingly employed in this indication. The theoretical advantages of these biomarkers are their direct measurement and prompt results.[9] However, among these molecules, various sensitivities and specificities have been reported from different studies in recent years.[10] Indeed, with its high sensitivity and specificity demonstrated in a large number of papers,[11,8,12] Alpha defensin quantitative detection (ADLF) was considered to be a powerful test for infection diagnosis, whereas other research groups reported[3] lower sensitivity, particularly in chronic infections, placing this test amongst the others.

We wondered if these differences were related to patient selection or differences in infection definitions. As such, we decided to assess the performance of the ADLF test in the diagnosis of chronic PJI in a series of chronic prosthetic infections using three classification systems: the MSIS criteria, Infectious Diseases Society of America (IDSA) criteria, [13] and European Bone and Joint Infectious Society (EBJIS) criteria.[14] Our hypothesis is that observed differences in sensitivity are not related to patient selection but to infection definition.

MATERIALS AND METHODS

The study was prospectively conducted between May 2015 and June 2016 in three different hospitals and approved by the institutional ethical review board. The patients provided written informed consent before their inclusion in the study. A standardized case report form was employed to collect patient data.

The inclusion criteria comprised chronic painful THA or TKA, suspected infection, or a workup for a failed THA or TKA, with adequate volume of synovial fluid collected and sufficient clinical data to perform the ADLF and other lab tests to fulfill the MSIS, EBJIS, and IDSA criteria.

The exclusion criteria were aspiration within 4 weeks after index operation, acute painful prosthesis, unicompartmental arthroplasties, and spacers.

The study population comprised 136 patients (40 in two centers and 56 in the other). The mean age of the included patients was 63 years. In 90 patients, a joint aspiration was performed. In the other 46 patients, the synovial fluid was collected during revision surgery. The latter patients had already undergone aspiration during pre-operative investigation but without using the alpha-defensin test (Figure 1).

Other parameters collected during the study were: erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), synovial fluid white blood cell count (SF-WBC), synovial fluid percentage of polymorphonuclear cells (SF-PMN). Cutoff values were as follow: ESR > 30m/h, CRP > 10 mg/L; WBC count on synovial fluid > 3000 and neutrophil ratio > 80%. No difference were done between hip and knee cutoffs. Bacteriological culture of the synovial fluid and periprosthetic tissues (at least three and no more than five samples) were taken for aerobic and anaerobic cultures with an incubation period of 14 days. A single pathogen of coagulase negative Staphylococcus, Propionibacterium acnes, or Corynebacterium was not considered to be an infection. On the other hand, Staphylococcus aureus positive isolates were classified as evidence of sepsis. Based on medical charts, biological parameters, and microbiology, the surgeon's intent-to-treat was classified as follows: treat as infected, or treat as non-infected. A positive histology was defined as the presence of ≥5 neutrophils per high-power field in ≥5 high-power fields (400x magnification).

The synovial fluid was obtained through a joint aspiration or by fluid collection during surgery. The Alpha Defensin Lateral Flow test (ADLF) (Synovasure®, Zimmer-Biomet, Warsow, Unites Sattes) was routinely carried out in the operating room. All staff involved in handling the collector vials and tests kits had been adequately trained. If the ADLF test was applied during revision surgery, the surgeon's intent-to-treat was recorded before the test results were made available. Allowance was made for the surgeon to change the operative plane as necessary[11].

Synovial fluid specimens were collected from TKAs by needle aspiration or aspiration before arthrotomy. In THAs, the specimens were obtained using image-intensified guided aspiration or aspiration through the joint capsule before arthrotomy in order to avoid blood soiling or contamination by skin flora. The synovial fluid was deposited in the dedicated ADLF receiver, and a microsafe tube was filled with 15 microliters of fluid by dipping it in the receiver. This fluid was added to the dilution buffer. Dilution of the synovial fluid and buffer was finalized by shaking the bottle. Finally, three drops of the diluted synovial fluid were applied to the test cassette. The result was read between 10 and 20 minutes following drop deposition. The test was positive when the control line and alpha-defensin line were both visible, with even the slightest line considered representative. A negative test result was confirmed when only the control line was present (Figure 2).

The ADLF test performance was assessed compared to the surgeon's intention to treat (ITT) and three classification systems: the MSIS criteria, IDSA criteria,[13] and EBJIS criteria (Table 1). [14]

Statistics were performed using the SigmaPlot 14.0 software from SPSS. The significance level was fixed at 0.05. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the ADLF results compared to the culture results, surgeon's ITT, and MSIS, IDSA, and EBJIS scores.

Correlations between the ADLF test and the culture results, surgeon's ITT, and MSIS, IDSA, and EBJIS scores were calculated using Spearman's correlation, with the coefficients rated as: 0–0.30 = little to no correlation, 0.30–0.5 = fair, 0.5–0.70 = moderate, and 0.70–1 = high correlation.[15] A Spearman's correlation was also calculated between the variable "ITT" and CRP, pus, sinus tract, culture, WBC, MSIS, IDSA, EBJIS, and ADLF values.

A Chi-squared test was conducted to compare the proportion of positive and negative values between the cultures and the MSIS, IDSA, EBJIS, and ADLF scores.

A multiple logistic regression was applied to identify the independent variables (age, gender, CRP, and SF-WBC count), predicting the probability of a positive culture. A ROC curve was used to determine a cut-off value pertaining to the independent variables predicting the probability of a positive culture.

RESULTS

The surgeon's intention to treat led 48 patients to a surgical revision for infection. 35 had a positive microbiological criteria concluding for infection and 40 had a positive alpha-defensin test. The MSIS, IDSA, and EBJIS criteria classified 41, 50, and 68 patients as infected, respectively. Considering the highest number of infected cases potentially identified with the EBJIS as a reference, 59% of the infections were simultaneously diagnosed by the three scores (Figure 3). Approximately 25% of the infections were only diagnosed by the EBJIS score. No infection was diagnosed by either the MSIS or IDSA scores, taken separately.

Table 2 provides the ADLF test's sensitivity and specificity. The weakest sensitivity was observed when the EBJIS criteria were used as a reference (55.8%; CI: 44.1-67.0), whereas the strongest sensitivity was recorded when the MSIS criteria were used as a reference (87.8%; CI: 74.4-94.6). No difference was observed between MSIS and MSIS 2018 scores. Using the IDSA score provided a moderate sensitivity result for ADLF (70%; CI 95%: 56.2-80.9).

The specificity results were proven strong (from 94% to 97%), no matter what diagnostic score was used. The correlations were moderate to strong between the test and the other tests (Table 3).

We did not observe any significant difference in proportion between the cultures and infections diagnosed by the MSIS score, IDSA score, or ADLF test, and the p-values were 0.499, 0.752, and 0.587, respectively. In contrast, there was a significant difference ($p < 0.001$) between the cultures and infections diagnosed by the EBJIS score.

The logistic regression results showed that the probability of positive culture results was significantly predicted by the WBC count (Figure 4). The WBC threshold value for a culture to be most at risk of being positive was also given by the ROC curve. The area under the

curve was greater than 0.9 ($p < 0.0001$). With a sensitivity of 91% and a specificity of 85% selected, the threshold value was 3,077 cells/microL. With a sensitivity of 80% and a specificity of 91% selected, the threshold value was 881 cells/microL.

Spearman's correlations coefficients between culture results, MSIS, IDSA, and EBJIS scores, ADLF test, WBC, CRP, pus, sinus tract, and surgeon's "ITT", are shown in Table 4. The correlation with the surgeon's "ITT" turned out to be strong with the MSIS criteria and moderate with the other results.

DISCUSSION

The diagnosis of a chronic PJI is based on the interpretation of multiple clinical and paraclinical data. In the absence of an absolute discriminant criterion, a surgeon must integrate all parameters in the history of their patient in order to establish the correct diagnosis and propose the appropriate treatment. In this context, alpha-defensin was one of the paraclinical elements based on which we tried to specify its diagnostic acuity.

We have confirmed the hypothesis of Trampuz et al.[3], suggesting that the sensitivity of the ADLF test is limited (56%–88%) depending on the diagnostic infection criteria that were used, implying that this test is not able to formally identify PJIs. However, its specificity was excellent (94%–97%, depending on the infection scores used), which reflects this test's high capacity to exclude the PJI diagnosis.

The contrasting results of the ADLF diagnostic performance based on the scores used in reference led us to evaluate the correlations existing between this rapid diagnostic test and the different diagnostic criteria sets. With a coefficient r at 0.84, the MSIS score correlated the most with the ADLF results, whereas the EBJIS score correlated much less, with a coefficient r equal to 0.58. These results have confirmed the variability of the diagnostic ADLF test's reliability according to the reference used.

However, we also found a low correlation of the EBJIS criteria with the bacteriological cultures (Chi-squared test showing a significant difference in the proportion of positive and negative results between the EBJIS criteria and cultures). In our cohort, though, every time a synovial fluid culture was shown positive, the infection was also diagnosed by the EBJIS criteria. Therefore, there was no case of "positive culture - negative EBJIS". The difference in the proportion of positive and negative results between the cultures and the EBJIS score, since existing according to the Chi-squared test, thus related to the "negative

culture - positive EBJIS" cases. As such, this reflected a tendency of the EBJIS score to overdiagnose the infections in relation to the synovial culture results. To corroborate this hypothesis, we performed a Kruskall-Wallis test that showed a significant difference between the number of diagnosed cases by the EBJIS score (n=68) and the number of diagnosed infection cases when using the MSIS score (n=41; p-value=0.004). The statistical test also showed that the EBJIS criteria induced more positive diagnoses than the MSIS (0.5 [0-1] vs 0[0-1]). Similar to Trampuz et al.,[3] we are thus able to discuss the fact that the EBJIS criteria tend to overdiagnose PJIs, making it possible to put into perspective the low ADLF Synovasure® test's sensitivity when the EBJIS criteria are taken as a reference.

Given this relative lack of ADLF sensitivity, we extracted the parameter with the highest correlation with the probability of a positive culture from our data. The logistic regression results showed the WBC count to be the most influential factor. The ROC curve also specified the values of this assay, presenting the best compromise between sensitivity/specificity. With a threshold value of between 1,000 and 3,000 cells/microL, we found similar results to the meta-analysis of Lee et al.[10] In the context of PJI diagnosis, as one limitation of this test's interpretation (*i.e.*, the determination of WBCs in synovial fluid in the immediate postoperative period) was avoided, we, therefore, recommend its use.

As each diagnostic tool ultimately has limitations in either its use or interpretation, it seemed interesting to highlight the one that was closest to the surgeon's therapeutic decision. In fact, beyond the diagnosis, the chosen treatment is likely to exert the most serious consequences on a patient's immediate future. Therefore, we sought to isolate the tool that most correlated with the surgeons' "ITT". Given this context, the Spearman's correlation showed that the MSIS criteria demonstrated a very good relationship with the final therapy. On the other hand, the EBJIS criteria also showed a moderate correlation with the surgeons' "ITT".

Limitations in the interpretation of our results must be mentioned. Firstly, a histological study was performed for only 41.2% of patients, and sonication was not available for any of the cohort's patients. Despite these conditions, the EBJIS and IDSA scores still diagnosed a larger number of infected patients than did the MSIS score. Intuitively, it can be assumed that the consistent contribution of histology and sonication would have reinforced the tendency of our study's findings, namely, more frequent positive diagnoses when using the EBJIS or IDSA scores as compared to the MSIS score. To illustrate this, we recalculated the EBJIS and IDSA scores in the patients who benefited from the histology analyses, without

considering their results, to establish the diagnosis. Of these 56 patients, 52 would have received an identical diagnosis whether or not the histology results were considered in the calculation of the EBJIS and IDSA scores. The four other patients had a different diagnosis for each of the two scores, depending on whether or not histology was considered, since histology was the only positive criterion for these patients. In these four cases, and when applying the EBJIS and IDSA scores, the histology data thus resulted in a further increase in the number of infections diagnosed.

Applying logistic regression to all the collected parameters, would have been ideal to find the most influencing factor for the likelyhood of a positive Culture. Nevertheless, the partial absence of histology and missing data in the calculation of the percentage of WBCs prevented the inclusion of these two parameters into logistic regression analysis. The WBC count still stood out at the end of this diagnostic test.

CONCLUSION

In conclusion, the ADLF test's sensitivity was proven to be limited in the detection of chronic PJIs, especially when the EBJIS criteria were used as a reference, whereas its specificity makes it an excellent diagnostic confirmation tool. However, we have moderated this statement by noting that, in our series, the EBJIS criteria were the least correlated with the probability of a positive culture, and that these criteria diagnosed the most infected prostheses. Therefore, we can hypothesize that the EBJIS criteria tend to overdiagnose chronic PJIs. This puts into perspective the lower diagnostic performance of ADLF in terms of sensitivity.

Parallel to this first conclusion, we obtained a good statistical behavior of the SF-WBC count. In addition, we also discovered a threshold value similar to those reported in the literature. In line with Trampuz and al.[3], we can further confirm here the usefulness of this assay in combination with the ADLF test for these specific virtues when the WBC count's interpretation limits have been reached.

Finally, it seems interesting to note that the MSIS criteria were the closest to the surgeons' ITT. In this context, these criteria represent the most reliable clinical and biological synthesis that an orthopedic surgeon has to elaborate when confronted with a possible PJI diagnosis.

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TABLES

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316 Table 1: Definitions of the Classification Systems for Diagnosing PJI [3]

MSIS (≥1 of the 2 Major Criteria OR ≥3 of 5 Minor Criteria)	IDSA (≥1 of the Following 4 Criteria)	Proposed Criteria of the EBJIS (≥1 of the Following 4 Criteria)
Major criteria:	Sinus tract communicating with the prosthesis	Purulence around the prosthesis or sinus tract
Two positive periprosthetic cultures	Purulence without other etiology surrounding the prosthesis	Increased synovial fluid leukocyte count
Sinus tract communicating with the prosthesis	Acute inflammation seen on histopathological examination of the periprosthetic tissue	Positive histopathology
Minor Criteria :	≥2 intraoperative cultures or combination of preoperative aspiration and intraoperative cultures yielding an indistinguishable organism	Confirmatory microbial growth in synovial fluid, periprosthetic tissue, or sonication culture
Elevated CRP and ESR		
Elevated synovial fluid leukocyte count or positive leukocyte esterase strip test		
Elevated synovial fluid percentage of granulocytes		
A single positive culture		
Positive histological analysis of periprosthetic tissue		

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320 Table 2: Sensitivity, specificity, positive predictive value (PPV), and negative predictive
321 value (NPV) of ADLF according to culture, ITT, MSIS, IDSA, and EBJIS criteria

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Diagnostic criteria	Positive patients /non infected patients	Positive patients / infected patients	Sensitivity (%) (CI: 5-95%)	Specificity (%) (CI: 5-95%)	PPV (%)	NPV (%)	Fiability (%)
MSIS	4 / 95	36 / 41	87.8 (74.4-94.6)	95.7 (89.4-98.3)	90	95.7	93.3
MSIS 2018	4 / 95	36 / 41	87.8 (74.4-94.6)	95.7 (89.6-98.3)	90	94.7	93.4
IDSA	5 / 86	35 / 50	70 (56.2-80.9)	94.2 (87.1-97.5)	87.5	84.3	85.3
EBJIS	2 / 68	38 / 68	55.8 (44.1-67.0)	97 (89.9-99.2)	95	68.8	76.5
ITT	4 / 88	36 / 48	75 (61.2-85.1)	95.4 (88.9-98.2)	90	87.5	88.2
Culture	10 / 101	30 / 35	85.7 (70.6-93.7)	90.1 (82.7-94.5)	75	94.8	88.9

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Table 3: Values of r (p value) of the Spearman's correlation between ADLF and MSIS, IDSA, EBJIS scores, and culture

	MSIS	IDSA	EBJIS	Culture
Synovasure ®	0.84 (p<0.001)	0.68 (p<0.001)	0.58 (p<0.001)	0.73 (p<0.001)

Table 4 : Values of r reflecting the Spearman's correlation between the surgeon's "intent-to-treat", ADLF result, MSIS, IDSA, EBJIS scores, culture, WBC, CRP, pus and sinus tract on the other hand

	Synovasure ®	MSIS	IDSA	EBJIS	Culture	WBC	CRP	Pus	Fistule
ITT	0.73	0.86	0.75	0.59	0.76	0.572	0.486	0.694	0.381

Figure legend page

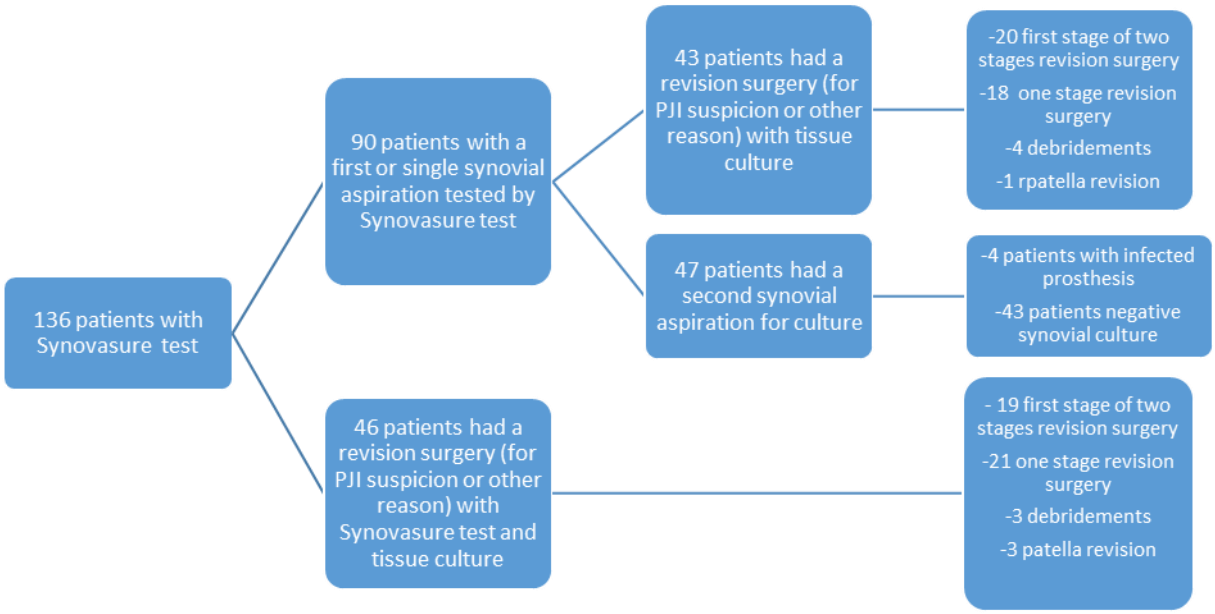
Figure 1: Flowchart of management in our 136 patient cohort with suspected infection

Figure 2: ADLF test

Figure 3: Frequencies of prosthetic infections diagnosed according to the MSIS, IDSA, and EBJIS classifications (expressed as a percentage of 68 infections diagnosed by these classifications)

Figure 4*:* ROC Curve illustrating the WBC's sensitivity and specificity according to its value

Figure 1: Flowchart of management in our 136 patient cohort with suspected infection



354 Figure 2: ADLF test

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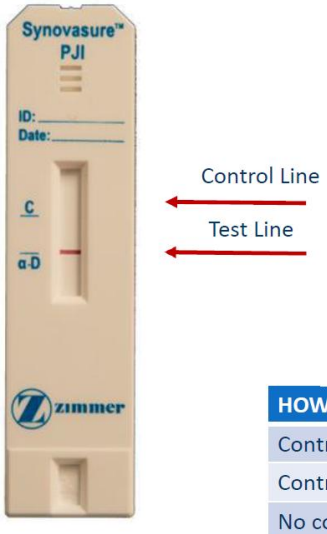

Control Line

Test Line

HOW DOES IT LOOK LIKE?	RESULT
Control line only	NEGATIVE
Control line + Test line	POSITIVE
No control line	INVALID TEST

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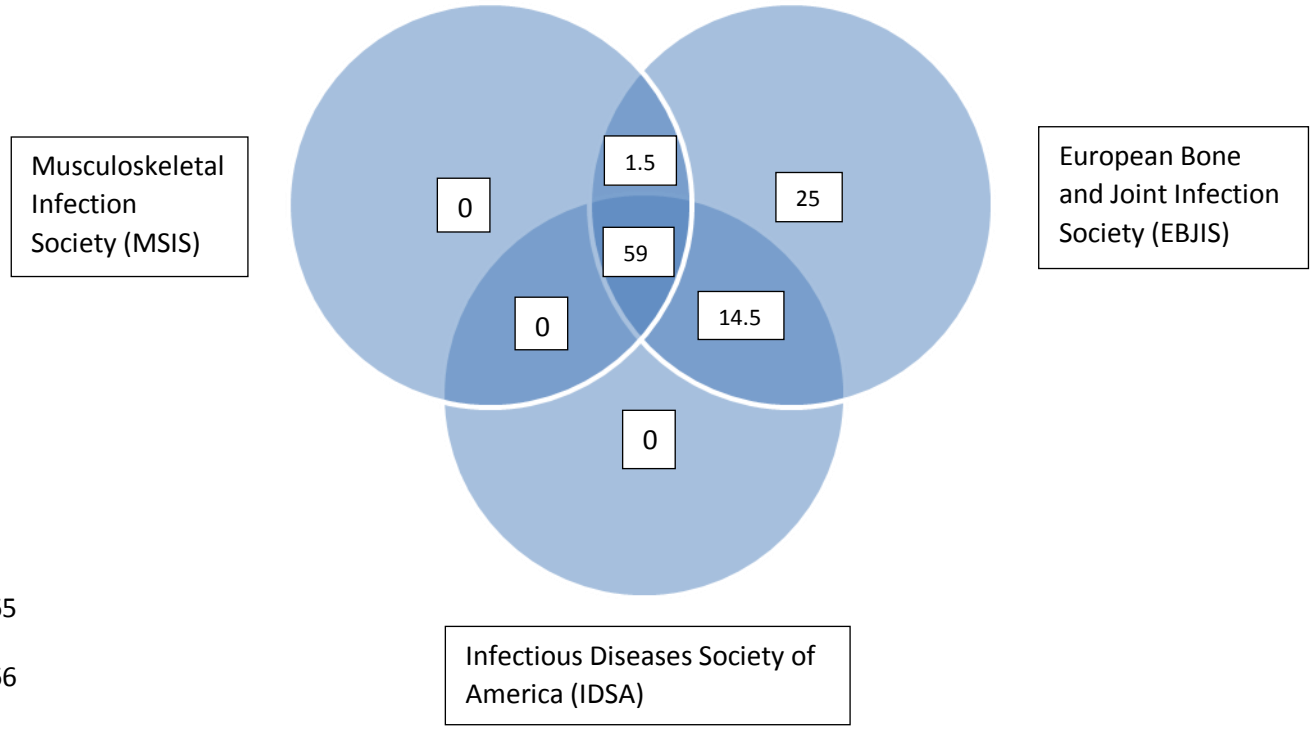
Figure 3: Frequencies of prosthetic infections diagnosed according to the MSIS, IDSA, and EBJIS classifications (expressed as a percentage of 68 infections diagnosed by these classifications)



368 Figure 4*:* ROC Curve illustrating the WBC's sensitivity and specificity according to its value

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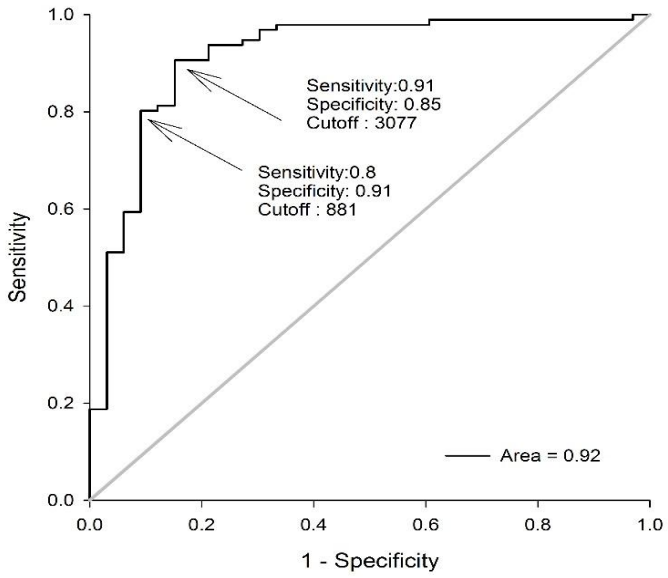

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