SYNOVIAL FLUID BIOMARKERS ASSOCIATED WITH SONICATION FLUID CULTURES IN THE DIAGNOSTIC OF PROSTHETIC JOINT INFECTIONS

RAREȘ MIRCEA BÎRLUȚIU[1], VICTORIA BÎRLUȚIU[2], RĂZVAN SILVIU CIȘMAȘIU[3], ANDRA MARIA BEBEȘELEA[4], PATRICIA MIHALACHE[5], MANUELA MIHALACHE[6]

[1,4,5,]PhD student, "Lucian Blaga" University of Sibiu, [2,6] "Lucian Blaga" University of Sibiu,
[3] "Carol Davila" University of Medicine and Pharmacy, Bucharest

Keywords: *prosthetic joint infection; PJI; cellular count of the synovial fluid; synovial leucocyte esterase; synovial C-reactive protein*

Abstract: *The context of a constant increase of the number of primary and revision total joint arthroplasty performed each year is associated with the increased risk of complication that is expected (both prosthetic joint infection and aseptic loosening). Having in mind this fact, the Academic Emergency Hospital Sibiu, Romania adopted and implemented, with the beginning of September 2016, a new strategy for the diagnosis of prosthetic joint infections, strategy that uses sonication fluid cultures and different synovial fluid biomarkers. The aim of this study was to evaluate the role of cellular count of the synovial fluid, leucocyte esterase, and C-reactive protein in synovial. The sensitivity and the specificity of the synovial fluid leukocyte count, % of neutrophils in the synovial fluid, synovial leucocyte esterase and synovial C-reactive protein were 73.33%/100%, 80%/85.71%, 80%/93.33%, 100%/86.66% respectively. In conclusion, bacteria culture of SF remains the gold standard (with a sensitivity and a specificity of 100%). Leucocyte esterase, synovial fluid leukocyte count, the % of neutrophils in the synovial fluid, and the synovial C-reactive protein represent a useful tool for rapid diagnosis of prosthetic joint infections. A diagnosis that remains a difficult one.*

INTRODUCTION

Total hip and knee arthroplasty are surgeries with a primary purpose of restoring the joint function. There are used in persons affected by osteoarthritis and increasingly used in the elderly population, that is a growing population, for both the treatment of the degenerative joint disease and also for femoral head fractures. Joint replacement surgeries have a significant effect on the quality of life, on the reduction of symptoms, on regaining physical function, and also on regaining the independence of daily routines and improving mobility.(1,2) An increased risk of complication is expected to be associated with the constant increase of the number of both primary and revision joint replacement surgeries that is seen in the last years (both prosthetic joint infection and aseptic loosening). Prosthetic joint infections are biofilm-related infection.(3)

The biofilm is a structure consisting of bacterial cells (one or more microorganism species), an aggregate of microorganisms, in which cells are surrounded by a matrix produced by the bacteria, a structure in which the cell that are adherent to each other and/or to a surface.(4) A correct and rapid diagnosis of the prosthetic joint infections is decisive for a correct therapeutic management. Diagnosis that based on a combination of clinical signs, laboratory data and imagistic studies, a diagnosis that still remains a difficult one. The therapeutic management of the cases of aseptic failure is different from the ones of prosthetic joint infections, and an accurate diagnosis is crucial for treatment outcome.(5) Prosthetic joint infections increase the hospitalization period and the cost of treatment for these patients.(6-8) Having in mind this fact, the Academic Emergency Hospital Sibiu, Romania adopted and implemented, with the beginning of September 2016, a new strategy for the diagnosis of prosthetic joint infections, strategy that uses sonication fluid cultures and different synovial fluid biomarkers.

PURPOSE

The aim of this study was to evaluate the role of cellular count of the synovial fluid, leucocyte esterase, and C-reactive protein in synovial.

MATERIALS AND METHODS

Study design

At the Academic Emergency Hospital Sibiu, Romania, a county hospital with 1054 beds, three intensive care unit services; general, vascular, thoracic surgery department, internal medicine, cardiology, neurology, hematology, oncology, infectious diseases department and orthopedic department, a single-center, observational, cohort, and ongoing study is conducted. An orthopedic department where around 1000 surgical procedures are performed each year, including primary interventions and revisions of joint prostheses. Before patient enrolment, the study protocol was approved by the institutional review board. We applied a strict diagnostic system to all the enrolled patients in the study, patients that underwent a surgical intervention of revision of a total joint prosthesis, to determine the cause of failure. In particular, to this study we implemented a diagnostic strategy that includes sonication of the removed prosthetic components or of an PMMA (polymethylmethacrylate) spacer and harvesting of the sonication fluid for bacteriological examination, cellular count of the synovial fluid, and the detection of leucocyte esterase, and C-reactive protein in synovial fluid.

Study population

Regarding the study population, in a prospectively manner we included all consecutive patients, with an aged over 18 years, hospitalized in our hospital, with the beginning of

[1]Corresponding author: Victoria Bîrluțiu, Str. Lucian Blaga, Nr. 2A, Sibiu, 550169, România, Email: victoriabirlutiu@yahoo.com, Phone +40269 215050
Article received on 01.02.2019 and accepted for publication on 29.03.2019
ACTA MEDICA TRANSILVANICA March 2019;24(1):66-70

September 2016 to the end of November 2017, patients who underwent a joint arthroplasty revision surgery. Detailed information was accessed from the medical records using a standardized data collection form. We evaluated the records for this specific study for the following data: demographic characteristics; laboratory, and microbiological data. For all the enrolled patients, the required information was available in full. We have followed the patients for a maximum of 28 months. Descriptive statistics was used to summarize the demographic; for each test, sensitivity, specificity, and predictive values were calculated; differences between prosthetic joint infection and aseptic loosening were evaluated by means of Student's t test for continuous variables (like serum CRP) and chi-squared test for categorized data (like leucocyte esterase), and we analyzed the data using PSPP, version 1.0.1. A p value ≤ 0.05 was considered statistically significant.

Study definitions and classification

Prosthetic joint infection was defined using criteria from the new definition for periprosthetic joint infection from the workgroup of the Musculoskeletal Infection Society published by Javad Parvizi et al.: and we used the classification proposed by Zimmerli et al, that defines the prosthetic joint infections as early (occurring within 3 months postoperatively), delayed (3-24 months) and late (> 24 months).(9) To determine whether or not there is an acute, late chronic or acute late prosthetic joint infection.

Synovial fluids studies

Synovial fluids were analyzed for cellular count, C-reactive protein, and leucocyte esterase. Preoperatively, synovial fluid was aspirated and transferred into two sterile vials. One of the vials contained EDTA for the determination of the leukocyte count and the percentage of granulocytes. The other was a vial for bacterial culture and it was a native one. After collection, samples were transported to the laboratory, where the vials were processed within 10-15 minutes. We assessed previous studies that have established the optimal cutoff points for the diagnosis of prosthetic joint infections with a synovial leukocyte count greater than >1.7 G/l or >65% neutrophils in knee prosthesis or leukocyte count >4.2 G/l or >80% neutrophils in hip prosthesis.(1,10) Regarding the detection of leucocyte esterase, we assessed the synovial fluid using enzymatic colorimetric strips (Dirui A10 Urine Analysis Reagent Strips, Dirui Industrial Co. Ltd, Changchun, China). To limit interference with the assays, between 1-4 ml of synovial fluid were centrifuged at 2500 rpm for 5 minutes. One drop of the resulted precipitate was placed on the pad for the detection of leucocyte esterase of the strip. The reaction was assessed according to the manufacturer. Production of purple color indicated a positive test. The determination of C-reactive protein from the synovial fluid was performed in an automated turbidimetric method using a specific reagent kit and on an ARCHITECT c4000 system (Abbott Laboratories, Illinois, U.S.A.).

Sonication of the retrieved implants. sonication fluid cultures

We retrieved both prosthesis implants or polymethylmethacrylate spacer and we sonicated them. In the operating theatre, saline sterile solution was added in the sterile containers, that were previously sterilized according to the manufacturer and packed in a double manner. We processed the implants within 20-30 minutes by sonication for 1 min using an ultrasound bath (BactoSonic®14.2, Bandelin GmbH, Berlin, Germany) at a frequency of 42 kHz and a power density of 0.22W/cm^2. 50ml of sonication fluid is centrifuged at 2500 rpm for 5 minutes after previously the resulted sonication fluid was vortexed. The resulted precipitate was inoculated onto Columbia agar with sheep blood (incubated aerobically, anaerobically and in high concentration of CO_2), Sabouraud plate, MacConkey agar plate, glucose broth, lactose broth and thioglycollate broth. Cultures are incubated at 37°C for 14 days and inspected in a daily manner for bacterial growth. Isolated bacteria are identified using the VITEK 2 Compact analyzer (bioMérieux, Marcy-l'Étoile, France). The MICs (minimum inhibitory concentrations) are assessed according to the EUCAST breakpoints. The sonication fluid cultures were considered positive, if >50 CFU/ml of sonication fluid were counted.(11-13)

RESULTS

Demographic characteristics of the enrolled patients

A total of 30 patients were enrolled in this study in the analyzed period (September 2016 to the end of November 2017), representing a total number of 30 retrieved implants, prosthesis (n=26) or polymethylmethacrylate spacers (n=4). The final diagnosis of aseptic failure was in 15 cases (50%) and prosthetic joint infections in 15 (50%) of the enrolled cases in the study. The 15 cases of prosthetic joint infections included patients with hip (n=6), knee (n=6) prosthesis and 3 patients with a prosthetic joint infection diagnosed after the sonication of hip PMMA spacers. Regarding the 15 cases of aseptic failure enrolled in our study, we were able to sonicate hip (n=13) prosthesis, and knee (n=2) prosthesis and 1 patient with a hip PMMA spacer. Regarding the age of the patients, the mean patient age at the time of the diagnosis of the prosthetic joint infection was 67 years (range, 56 to 83 years), and 9 (60%) were male patients. The mean patient age at the time of revision of the aseptic failure cases was 63 years (range, 44 to 79 years), and 8 (53.33%) were male patients. Among the 15 prosthetic joint infections cases, 2 (12.5%) were early postoperative, 4 (25%) were delayed postoperative (low-grade) and 9 (60%) were late infections. The two groups did not significantly differ for gender ratio or age.

Laboratory data of the enrolled patients

Erythrocytes sedimentation rate (ESR), and serum C-reactive protein (CRP), were determined at all the enrolled patients in the study. The mean ESR (reference value 0-15 mm/h) values for the prosthetic joint infection cases and aseptic loosening cases were 41.5 mm/hour and 26.1 mm/hour, respectively. The mean serum CRP (reference value <6 mg/dl) values for prosthetic joint infection and aseptic loosening cases were 36 mg/L (range, 7 to 70) and 8 mg/L (range, 0 to 25), respectively. The serum CRP level was higher in the prosthetic joint infections group than in aseptic loosening one. The erythrocyte sedimentation rate was markedly lower at the aseptic loosening patients than in the prosthetic joint infections group. The two groups did not significantly differ for ESR rate but were significantly differ for serum CRP level ($p < 0.002$).

Synovial fluid study

From the retrieved synovial fluid, cellular count of the synovial fluid, detection of leucocyte esterase, and C-reactive protein were performed. All three studied parameters were higher in the prosthetic joint infections group than in aseptic loosening one, and all three being significantly differ. Regarding the mean total synovial fluid leukocyte count for the prosthetic joint infection cases it was 13 G/L (range, 3.2 – 29) and for the aseptic loosening cases it was 0.6 G/L (range, 0.2-1), $p < 0.001$. The assessment of the % of neutrophils was in the prosthetic joint infection cases 70% (range, 42-95%) and in the aseptic loosening cases 43.2% (range, 0 to 70%), $p < 0.002$.

For the 30 patients included in our study, we were able to obtain enough synovial fluid for the leucocyte esterase strip test for all enrolled patients in the study. For the aseptic

loosening group, the strip test was positive for one patient and it was graded as + and for the rest of the patients it was negative (n=14), in contrast with the prosthetic joint infection group, the leucocyte esterase strip test was negative in three cases (one delayed infection and 2 late infections) and was positive as + or ++ in 12 patients (p<0.00 septic versus not septic patients).

Finally, the mean C-reactive protein in synovial fluid for the prosthetic joint infection cases was 34 mg/L (range, 12 – 63) and for the aseptic loosening cases was 2.55mg/l (range, 0-7). C-reactive protein was significantly higher in the infected patient group than in the aseptic loosening patients group (p <0.003).

Microbiologic characteristics

Microbial growth was observed in all cases of prosthetic joint infections. From the sonication fluid culture, a single causative agent was isolated in 13 (86.6%) and a polymicrobial infection in 2 (13.3%) cases. We were able to isolate the following strains: *Staphylococcus epidermidis* (n=4; >1000CFU/ml); *Staphylococcus lentus* (n=1, >50CFU/ml); *Staphylococcus xylosus* (n=1, >50CFU/ml); *S. aureus* (n=3, >1000CFU/ml); *Enterococcus faecalis* (n=2, >50CFU/ml); *Ralstonia pickettii* (n=2, >50CFU/ml); *Enterobacter spp.* (n=1, >50CFU/ml); *Klebsiella spp.* (n=1, >50CFU/ml), *Pseudomonas spp*. and (n=1, >50CFU/ml).

Comparison of diagnostic techniques

The performance of the used diagnostic methods is summarized in table no. 2. The synovial C-reactive protein test showed the best performances in terms of sensitivity, followed by leucocyte esterase strip test, % of neutrophils in the synovial fluid, and synovial fluid leukocyte count. Regarding the specificity of the used tests, synovial fluid leukocyte count showed the best performances followed by leucocyte esterase strip test, synovial C-reactive protein test, and % of neutrophils in the synovial fluid. Compared with the used tests, culture of the sonication fluid still remains the gold standard in diagnosing prosthetic joint infections with the sensitivity and specificity of 100%.

Table no. 1. Performance of used diagnostic methods

Diagnostic method	% sensitivity (95% CI)	% specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)
Synovial fluid leukocyte count	73.33(48.05-89.10)	100.00(79.61-100.00)	-	0.267(0.115-0.617)
% of neutrophils in the synovial fluid	80.00(54.84-92.95)	85.71(60.06-95.99)	5.6(1.514-20.709)	0.233(0.083-0.657)
Leucocyte esterase	80.00(54.84-92.95)	93.33(70.18-98.81)	12(1.776-81.064)	0.214(0.077-0.595)
Synovial C-reactive protein	100.00(79.61-100.00)	86.67(62.12-96.26)	7.5(2.064-27.252)	0
Culture of the sonication fluid	100.00 (79.61-100.00)	100 (79.61-100.00)	-	-

DISCUSSIONS

Prosthetic joint infections represent serious complication of total joint arthroplasty and require early, rapid, and accurate diagnosis. The diagnosis of PJI relies on a series of criteria.(1,14,15) Until this moment, there is no clearly defined standard for the diagnosis of prosthetic joint infection.(16) It is mandatory for the management of prosthetic joint infections cases, a multidisciplinary approach.(1) Associated with conventional microbiological methods like culture, prosthesis sonication and molecular methods are definitely improving the diagnostic performances.(17)

Leukocyte esterase is an enzyme primarily secreted by neutrophils, as in cases with PJIs, neutrophils will secrete leukocyte esterase around an infected joint (18), leukocyte esterase strip test has been used for the diagnosis of urinary tract infections (UTIs) since the early 1980s (19-21) and it has been reported to have good sensitivity and specificity.(22) In 2011, Parvizi et al. were the first to show that the LE strip test demonstrates high sensitivity and specificity for the diagnosis of prosthetic joint infections in the knee joint. The leukocyte esterase strip test is a rapid test, with results that can be obtained in two or three minutes.(18) Many studies have confirmed the reliability of the leukocyte esterase strip test.(22-26) Since 2014, with the modified diagnostic criteria of the MSIS, a positive LE test is considered to be a minor criterion, and it is equivalent to the synovial white blood cell (WBC) count.(14)

In our study, the LE strip test had a sensitivity of 80% (95% CI, 54.84-92.95%) and a specificity of 93.33% (95% CI, 70.18-98.81%). Parvizi et al reported sensitivity and specificity of 80.6% (95% CI, 61.9–91.9%) and 100% (95% CI, 94.5–100.0%), respectively (18), and they also showed its correlation with the percentage of polymorphonuclear leucocytes and total white blood-cell count in synovial fluids. Similar data to ours was reported also by Li et al, they reported a sensitivity of 92.1% (95% CI, 77.5–97.9%) and a specificity of 96.4% (95% CI, 86.4–99.4%).(27) Wang et al reported a sensitivity of 90% and a specificity of 97%.(28) De Vecchi et al, reported in there study a 92.6% specificity and a sensitivity of 97%, that was similar to what we were able to find in our study for leucocyte esterase.(29)

Regarding the synovial C-reactive protein it showed a higher sensitivity and lower specificity with respect to LE. It is suggested that serum CRP is likely to diffuse into joint fluid thanks to alterations in synovial permeability, as a result of the inflammatory process caused by infection.(29,30). Different cut-off values for CRP have been reported ranging between 2.5 and 9.5 mg/L (29-32), which were associated with variable sensitivity and specificity. We used a cut-off limit of 6 mg/L, which allows us to obtain acceptable specificity and sensitivity. De Vecchi et al, reported in there study a 81.5% specificity and a sensitivity of 94.1%.(29)

In our study, the synovial fluid leukocyte count had a sensitivity of 73.33% (95% CI, 48.05-89.10%) and a specificity of 100% (95% CI, 79.61-100%) and the % of neutrophils in the synovial fluid had a sensitivity of 80% (95% CI, 54.84-92.95%) and a specificity of 85.71% (95% CI, 60.06-95.99%). Dinneen et al reported for the synovial white cell count a sensitivity of 89.5% and a specificity of 91.3%, higher values then ours, and for the % of neutrophils in the synovial fluid higher then the cut-off value, a sensitivity of 89.7% and a specificity of 86.6% similar values to our data.(33) Trampuz et al aimed to define cut-off values for synovial fluid leukocyte count and % of neutrophils in the synovial fluid that would reliably indicate prosthetic joint infection in revision TKRs. Using the same values a higher sensitivity (94%) but a lower specificity (88%) were reported with similar specificity and sensitivity regarding the % of neutrophils in the synovial fluid as ours.(10) Ghanem et al reported from a study of 429 cases with different cut-off values (>1100 white cells/µl of which > 64% were neutrophils), a slightly higher sensitivity (90.7%) but again a lower specificity (88.1%).(34)

The analysis of cultures of the sonication fluid samples from the published data, showed a wide range of performances. Despite the absence of a reference standard, it still remains difficult to assess the sensitivity and specificity values of sonication fluid culture that ranges from 50% to 92% and from 65% to 94%, respectively.(35) In our study, sonication fluid culture had the best performance.

Obviously, also this study has some limitations: the first one is the limited studied population, respectively the limited population with prosthetic joint infections enrolled in the study. Our center is not dedicated to the treatment of prosthetic joint infections, but with the introduction of the new protocol and with the dedicated team that is managing these cases (orthopedic surgeon – infectious disease specialist – microbiologic), the prevalence of prosthetic joint infections in our population might be higher. It is a single center study. The analyzed methods in this study have there one limitations, like the leucocyte esterase strip test has difficulties in reading color development due to the presence of blood or debris. Larger studies are needed to confirm these results. Nevertheless, our results are very promising.

CONCLUSIONS

In conclusion, bacteria culture of sonication fluid remains the gold standard in diagnosing prosthetic joint infections. The leukocyte esterase strip test was found to have almost similar results to synovial C-reactive protein, having in mind that it is a more rapid test and is less costly, it is a good option compared with the costs of the synovial C-reactive protein detection. The published data regarding the synovial C-reactive protein shows that each center should establish their own cut-off points because as reported by other authors, its determination seems to be affected by the method used. Both leucocyte esterase and synovial C-reactive protein have high diagnostic value for diagnosing prosthetic joint infection. Both synovial fluid leukocyte count and the % of neutrophils in the synovial fluid maintain their role in the diagnostic of prosthetic joint infection. The detection of leucocyte esterase, synovial fluid leukocyte count and the % of neutrophils in the synovial fluid is reliable and valid being part of the current battery tests for the detection of prosthetic joint infections according to the new International Consensus on Orthopedic Infections criteria, the role of the synovial C-reactive protein still needs to be assessed.

REFERENCES

1. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Executive Summary: Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1):1-10.
2. Douglas RO, Elie FB, Anthony RB, Daniel L, Werner Z, James MS, et al. Executive Summary: Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clinical Infection Diseases. 2013;56(1):1-10.
3. Wolcott R, Ehrlich G. Biofilm and chronic infections. JAMA. 2008;299(22):2682-4.
4. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol. 2016;14(9):563-75.
5. Del Pozo JL, Patel R. Clinical practice. Infection associated with prosthetic joints. N Engl J Med. 2009;361(8):n787e94.
6. Xu Y, Larsen LH, Lorenzen J, Hall-Stoodley L, Kikhney J, Moter A, et al. Microbiological diagnosis of device-related biofilm infections. APMIS. 2017;125(4):289-303.
7. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013;173(22):2039-46.
8. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(5):625-63.
9. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351(16):1645–54.
10. Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med. 2004;117(8)117:556–52.
11. Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. N Engl J Med. 2007;357(7):654e63.
12. Achermann Y, Vogt M, Leunig M, Wust J, Trampuz A. Improved diagnosis of periprosthetic joint infection by multiplex PCR of sonication fluid from removed implants. J Clin Microbiol. 2010;48(4):1208e14.
13. Birlutiu RM, Roman MD, Cismasiu RS, Fleaca SR, Popa CM, Mihalache M, et al. Sonication contribution to identifying prosthetic joint infection with Ralstonia pickettii: a case report and review of the literature. BMC Musculoskelet Disord. 2017;18(1):311.
14. Parvizi J, Gehrke T. Definition of periprosthetic joint infection. J Arthroplasty. 2014;29(7):1331.
15. Della Valle C, Parvizi J, Bauer TW, Dicesare PE, Evans RP, Segreti J, et al. Diagnosis of periprosthetic joint infections of the hip and knee. J Am Acad Orthop Surg. 2010;18(12):760-70.
16. Oussedik S, Gould K, Stockley I, Haddad FS. Defining peri-prosthetic infection: do we have a workable gold standard? J Bone Jt Surg Br. 2012;94(11):1455-6.
17. Corvec S, Portillo ME, Pasticci BM, Borens O, Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. Int J Artif Organs. 2012;35(10):923-4.
18. Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of periprosthetic joint infection: the utility of a simple yet unappreciated enzyme. J Bone Joint Surg Am. 2011;93(24):2242-8.
19. Perry JL, Matthews JS, Weesner DE. Evaluation of leukocyte esterase activity as a rapid screening technique for bacteriuria. J Clin Microbiol. 1982;15(5):852–4.
20. Smalley DL, Dittmann AN. Use of leukocyte esterase-nitrate activity as predictive assays of significant bacteriuria. J Clin Microbiol. 1983;18(5):1256-7.
21. Chernow B, Zaloga GP, Soldano S, Quinn A, Lyons P, McFadden E, et al. Measurement of urinary leukocyte esterase activity: A screening test for urinary tract infections. Ann Emerg Med. 1984;13(3):150–4
22. Berger RE: The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. J Urol. 2005;174(3):941–2.
23. Wetters NG, Berend KR, Lombardi AV, Morris MJ, Tucker TL, Della Valle CJ. Leukocyte esterase reagent strips for the rapid diagnosis of periprosthetic joint infection. J Arthroplasty. 2012;27(8 Suppl.):8–11.
24. Tischler EH, Cavanaugh PK, Parvizi J. Leukocyte esterase strip test: Matched for musculoskeletal infection society criteria. J Bone Joint Surg Am. 2014;96(22):1917–20.
25. Colvin OC, Kransdorf MJ, Roberts CC, Chivers FS, Lorans R, Beauchamp CP, et al. Leukocyte esterase analysis in the diagnosis of joint infection: Can we make a diagnosis using a simple urine dipstick? Skeletal Radiol. 2015;44(5):673–7.
26. Shafafy R, McClatchie W, Chettiar K, Gill K, Hargrove R, Sturridge S, et al. Use of leucocyte esterase reagent strips in the diagnosis or exclusion of prosthetic joint infection.

Bone Joint J. 2015;97-b(9):1232–6.
27. Li R, Li X, Yu B, Li X, Song X, Li H, et al. Comparison of Leukocyte Esterase Testing of Synovial Fluid with Synovial Histology for the Diagnosis of Periprosthetic Joint Infection. Med Sci Monit. 2017;23:4440-6.
28. Wang C, Li R, Wang Q, Wang C. Synovial Fluid Leukocyte Esterase in the Diagnosis of Peri-Prosthetic Joint Infection: A Systematic Review and Meta-Analysis. Surg Infect (Larchmt). 2018;19(3):245-253.
29. De Vecchi E, Villa F, Bortolin M, Toscano M, Tacchini L, Romanò CL, et al: Leucocyte esterase, glucose and C-reactive protein in the diagnosis of prosthetic joint infections: A prospective study. Clin Microbiol Infection. 2016;22(6):555–60.
30. Parvizi J, McKenzie JC, Cashman JP. Diagnosis of periprosthetic joint infection using synovial C-reactive protein. J Arthroplasty. 2012;27(8 Suppl):12-6.
31. Tetreault MW, Wetters NG, Moric M, Gross CE, Della Valle CJ. Is synovial C-reactive protein a useful marker for periprosthetic joint infection? Clin Orthop Relat Res. 2014;472(12):3997-4003.
32. Omar M, Ettinger M, Reichling M, Petri M, Guenther D, Gehrke T, et al. Synovial C-reactive protein as a marker for chronic periprosthetic infection in total hip arthroplasty. Bone Joint J. 2015;97-B(2):173-6.
33. Dinneen A, Guyot A, Clements J, Bradley N. Synovial fluid white cell and differential count in the diagnosis or exclusion of prosthetic joint infection. Bone Joint J. 2013;95-B(4):554-7.
34. Ghanem E, Parvizi J, Burnett RS, Sharkey PF, Keshavarzi N, Aggarwal A, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. J Bone Joint Surg Am. 2008;90(8):1637-43.
35. Malandain D, Bémer P, Leroy AG, Léger J, Plouzeau C, Valentin AS, et al. Assessment of the automated multiplex-PCR Unyvero i60 ITI® cartridge system to diagnose prosthetic joint infection: a multicentre study. Clin Microbiol Infect. 2018;24(1):83.e1-83.e6.