Full paper

Intraoperative diagnosis of *Staphylococcus aureus* and coagulase-negative Staphylococcus using Xpert MRSA/SA SSTI assay in prosthetic joint infection

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SUMMARY

The aim of this prospective study was to evaluate the performance of the Polymerase Chain Reaction (PCR) tool Xpert MRSA/SA SSTI test (Cepheid, Sunnyvale, CA, USA) on periprosthetic samples from a cohort of patients with suspected prosthetic joint infection (PJI).

Seventy adult patients were included in this prospective study. On the basis of the preoperative evaluation, 39 patients were clinically considered to have a PJI, whereas 31 were presumed to suffer from an aseptic mobilization of the implant. Xpert MRSA/SA SSTI identified 4 out of 4 MRSA, 7 out of 7 MSSA, and 14 out of 16 methicillin resistant CoNS.

Among the 31 patients not having a PJI, the rapid PCR did not find any bacteria among those identifiable, thus demonstrating an excellent performance in terms of specificity. Statistical analysis of the analytical performance showed a high correlation ($p < 0.001$) between the result of Xpert MRSA/SA SSTI and culture.

Xpert MRSA/SA SSTI assay is a novel, yet well known, rapid and accurate method for the identification of different species of staphylococci. The test can be used with peri-operative samples thus dramatically improving the diagnostic sensitivity. In addition, thanks to the very short turnaround time the use of Xpert assay can modify the clinical management of patients suffering from PJI during the ongoing operative procedure.

Key words: Prosthetic joint infection, Rapid diagnosis, PCR, *Staphylococcus aureus*

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INTRODUCTION

The incidence of prosthetic joint infection (PJI) for knee and hip has been increasing in recent years as a result of the growing number joint replacements, thus creating an economic burden on the health system of most Western countries. (Kurtzu et al., 2012) The diagnosis of PJI is sometimes challenging (Del Pozo and Patel, 2009; Osmon et al., 2013) and although many different clinical parameters can suggest an infection, only the identification of the infecting microorganism provides the diagnosis with the highest level of certainty.

In the case of suspected infection, bacteria can be detected by different methods. The isolation of pathogens by culture of tissue samples is still the gold standard (Achermann et al., 2010; Trampuz et al., 2007). Culturing the biological material dislodged from the surface of the implant with the application of ultrasound-generated power or treating the implant with dithiothreitol have both been recently reported to increase the sensitivity of organism recovery (Drago et al., 2012; Trampuz et al., 2007). Despite improved sensitivity, culture-negative cases remain and this prevents determination of the true presence of infection. Another major problem is the delay in obtaining a result, which can vary from 2 days to 3 weeks (Schafer et al., 2008). *Staphylococcus aureus* (SA) and the group of coagulase-negative staphylococci (CoNS) are the main pathogens for PJI (ECDC, 2013) and the identification of the methicillin resistance phenotype (MR) is mandatory in order to start correct antibiotic therapy as soon as possible (Trampuz and Zimmerli, 2008).

Compared to culture, real-time polymerase chain reaction (PCR) is indeed faster and theoretically more sensitive, especially when patients are treated with antibiotics before being sampled, a well-known situation that reduces the sensitivity of culture-based methods. However, the routine use of molecular techniques in the diagnosis of PJI has been limited to selected settings by costs and complexity of the workflow (Achermann et al., 2010; Dubouix-Bourandy et al., 2011; Kobayashi et al., 2009)

The Xpert® MRSA/SA SSTI assay (Cepheid, Sunnyvale, CA, USA) performed on the GeneXpert® instrument is a new generation test based on multiplex Real Time –PCR technology that can simultaneously detect 3 targets: staphylococcal protein A (*spa*) gene, the gene for methicillin resistance (*mecA*) and the staphylococcus cassette chromosome (*SCCmec* junction region in the staphylococcal chromosome). An internal control (SPC) (*Bacillus globigii*) is also simultaneously amplified during each diagnostic procedure to detect inhibition and proper amplification. This test is rapid (56 minutes), does not require specific technical skills and has excellent sensitivity (94.4%) and specificity (100%), as reported in the literature (Wolk et al., 2009a; 2009b). Even if the Xpert MRSA/SA SSTI assay is not validated for the detection of CoNS, when only the *mecA* gene is identified there is a strong indication of the presence of a MR CoNS.

The aim of this prospective study was to evaluate the performance of the Xpert MRSA/SA SSTI test on periprosthetic samples collected by E-swab (Copan, Brescia Italy) obtained from a cohort of patients with suspected chronic PJI and to compare the results of the molecular method with those obtained by the standard diagnostic procedure based on cultures of periprosthetic tissue samples and sonication fluids from the surface of the devices.

MATERIAL AND METHODS

Between February and November 2015, 70 adult (> 18 yo) patients who underwent removal of at least one component of hip or knee arthroplasty due to septic or aseptic loosening were included in this prospective study. Patients with rupture of the prosthesis or affected by a periprosthetic fracture were excluded. The study was approved by the local ethics committee (Istituto Ortopedico Rizzoli, Bologna, Italy).

Preoperatively, all information on the location and the type of prosthesis, the clinical presentation, laboratory tests (ESR and CRP, leukocyte parameters, fibrinogen) and nuclear diagnostics (scintigraphy with labeled leukocytes) were recorded for each patient enrolled. According to the clinical presentation (presence of a fistula communicating with the implant), patients were considered to have a septic mobilization. In the absence of fistula and in the presence of elevated ESR> 30 mm/h and CRP> 1 mg/dl, a joint aspiration was performed for examination and patients were considered to have suspected septic or aseptic failure based on the aspirate leukocyte count (leukocytes > 3000 per microliter, with > 80% neutrophils).

During the surgery, at least 5 separate biopsies from periprosthetic tissue were collected. All prosthetic components were removed in the operating room under sterile conditions and transported to the microbiology laboratory where they were processed with ultrasound treatment. All the samples were collected intra-operatively before any empiric antibiotic therapy was started.

The fluids obtained by sonication and the periprosthetic samples were cultured using beadmill processing to isolate all the microorganisms present (Roux et al., 2011; Trampuz et al., 2007) Both aerobic and anaerobic cultures at 7 and 14 days and sensitivity test to antimicrobial drugs were performed (Molina-Manso et al., 2013).

One Eswab from the periprosthetic tissue from each patient was collected and placed in the Eswab Amies transport medium in the Eswab vial before the prosthesis was removed. Each Eswab was placed into a sampler reagent vial from the Xpert kit, vortexed for 10 seconds, and then transferred into an Xpert® MRSA/SA SSTI cartridge directly in the operating theatre.

Patients were diagnosed to have a PJI when at least one of the following criteria was present: a) a sinus tract communicating with the prosthesis; b) the same microorganism isolated in at least 2 samples (at least in 1 sample with bacterium not belonging to the cutaneous flora, such as SA); c) at

least four of the following six elements: 1. acute inflammation on the intra-operative histological examination (at least 5 neutrophils per field at high magnification); 2. presence of pus in the joint; 3. microorganism isolated in only one of five biopsies; 4. increased white blood cell count of aspirated joint fluid > 3000 per microliter; 5. increased percentage of neutrophils in aspirated joint fluid > 80%; 6.ESR> 30 mm/h and CRP> 1 mg / dl (Parvizi et al., 2011).

Differences between the results obtained by culture-based techniques and those of PCR were assessed by the log-rank test. P values <0.05 were considered significant. All analyses were completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY,USA).

RESULTS

Seventy patients were included in this prospective study (39 males and 31 females). The median age was 70 years (range, 18-88); 42 (60%) patients had a hip prosthesis, 28 (40%) a knee prosthesis. On the basis of the preoperative evaluation, 39 (56%) of these patients were clinically considered to have a PJI, whereas 31 (44%) were presumed to suffer from an aseptic mobilization of the implant.

Thirty-seven patients considered to have a septic mobilization of the implant on clinical evaluation were confirmed to have a PJI according to previously described criteria (presence of fistula, blood and joint tests and cultures of sonication fluid and biopsy samples). (Table 1)

In 9 cases, the culture-based diagnosis demonstrated the presence of bacteria (MS CoNS in 3 cases, *Streptococcus agalactiae* in 2 cases and *Streptococcus gordonii, E.aerogenes, E.faecalis*, and *Pseudomonas aeruginosa* in 1 case each): all these species are not detectable by the Xpert MRSA/SA SSTI assay and were therefore excluded from the final evaluation of the performance of this test. In one additional patient neither cultural examination nor PCR test identified the pathogen responsible but PJI was confirmed by the presence of a fistula communicating with the implant. All these patients but one with MR *Staphylococcus epidermidis* responsible for PJI had been considered septic at pre-operative evaluation.

Xpert MRSA/SA SSTI identified 4 out of 4 MRSA and 7 out of 7 MSSA. Patients with SA infection had a mean of 3.8 cultures positive for the same bacteria (range, 2-5). Those patients with MSSA PJI had antibiotic therapy changed directly in the OR, thus reducing the empiric use of daptomycin of a mean of 6.3 days (range 5-8).

In addition, MR CoNS were extrapolated by the amplification of *mecA* gene only with the final identification of 14 out of 16 bacteria which were present on cultures (mean 3.6, range 3-5). In 2 cases the rapid PCR did not identify the pathogen responsible for PJI (MR CoNS identified on cultural examination performed on 4 and 5 samples respectively). Both these patients had

laboratory values suggestive for PJI (ESR>50mm/h and CRP>2.5 mg/dl). Among 31 patients not having a PJI, rapid PCR did not find any *Staphylococcus*, yielding excellent performance in terms of specificity.

Statistical analysis of the performance did not show any difference between Xpert MRSA/SA SSTI PCR and culture performance, but a high correlation (P <0.001).

DISCUSSION

In the present series we observed a higher sensitivity of the culture-based diagnosis compared with data reported in the literature and this can be explained by our combination of cultures performed on periprosthetic tissue samples and on the fluid derived from sonication of the prosthesis in order to define PJI with certainty (Parvizi et al., 2011; Portillo et al., 2014).

Staphylococcus aureus and CoNS were found to be responsible for the majority of PJI, as previously reported in the literature (ECDC, 2013; Lewis et al., 2015). However, in the present series 9 (24%) infections were attributable to other bacterial species and these were obviously missed by the PCR-based method that is limited to the detection of staphylococci.

When considering exclusively the patient population with confirmed infection by *SA*, the Xpert assay showed a high sensitivity and specificity, as previously reported in other studies that included also septic arthritis and spondylodiscitis patients (Dubouix-Bourandy et al., 2011; Lourtet-Hascoett et al., 2015; Titecat et al., 2012; Valour et al., 2014) (Table 2). Our results highlighted the performance of the Xpert MRSA/SA SSTI assay for the rapid identification of *SA* (including *mecA*) directly from the periprosthetic samples obtained and processed directly in the operating theatre. Furthermore, in the present study we also observed good performance of this molecular test for the identification of *mecA* bearing CoNS, even if slightly lower accuracy than that observed for MRSA and MSSA.

Empirical treatment covering most pathogens causing PJI is generally started soon after surgery in order to prevent a negative outcome and it is continued until an antimicrobial sensitivity test (AST) result becomes available. Since staphylococci are the most frequently bacteria isolated in PJI, recommendations for empirical treatment include agents that have high activity against these species, such as daptomycin, which is associated with various side effects and must be administered at doses higher than 6 mg/kg for long periods after the implant has been removed (Byren et al., 2012; Corona Perez-Cardona et al., 2012; Sousa et al., 2010) (Figure 1). Therefore an Xpert MRSA/SA SSTI positive result allows clinicians to rapidly adapt the antimicrobial therapy with penicillin active against staphylococci for MSSA or to appropriately maintain daptomycin for MRSA, therefore leading to reduced cost of overall patient management, decreased length of hospital stay, and diminished rate of potential adverse events (Gray et al., 2012; Muszbek et al.,

2013). Last but not least, more appropriate use of pathogen-driven therapy could contribute to the reduction of emergence of resistant bacteria (Parta et al., 2010). Furthermore, higher failure rates have been seen in infections by MRSA and the early identification of high-risk patients may help in determining more adequate treatment (Bradbury et al., 2009).

Conventional PCR tests have some limitations that hamper the use of these methods in the routine diagnosis of PJIs. First of all, nearly all PCR assays involve complex and time-consuming analytical processing, making them impractical for routine rapid clinical use (Achermann 2010; Rosey et al., 2007; Yang et al., 2008). Secondly, the use of broad-range 16S rRNA gene PCR can detect previously unknown organisms but has lower sensitivity than specific PCR and fails to detect antimicrobial resistance (Hombach et al., 2010). In comparison, the GeneXpert system delivers reports directly from unprocessed samples, requires only reduced technical time of non-specialized personnel, and requires no specific separated technical area. In fact, in the present study the test was performed directly in the operating room by trained nursing personnel, with a response within less than 1 hour after the test was started.

Another potential practical use of the Xpert MRSA/SA SSTI assay should be considered. In the case of revision arthroplasty, it is of paramount importance to have as many observations as possible to exclude the presence of bacteria at the time of re-implantation (Chen et al., 2014). Due to its high sensitivity and specificity both for *SA* and *MR* CoNS, the Xpert assay might be used at the time of re-implantation in the 2-stage procedure, in association with intra-operative histopathological examination in cases in which *SA* or MR CoNS had been previously isolated from cultures at the time of the removal of the prosthesis.

The development of automated multiplex PCR assays detecting a larger panel of microrganisms commonly causing PJI such as *mecA* negative CoNS and *Propionibacterium acnes* might extend the use of Xpert also in the case of the 1-stage revision arthroplasty (Kunutsor et al., 2016). Until such a test is available, conventional cultures remain the reference method for the diagnosis of non-staphylococcal and/or plurimicrobial PJI.

We conclude that the Xpert MRSA/SA SSTI assay is a novel, yet well known, rapid, and accurate method for the determination of different species of staphylococci and their genetic resistance determinants to methicillin in peri-operative samples that can dramatically improve the diagnosis and the clinical management of patients suffering from bone and joint infections, as it can detect the most common species, as well as resistance to methicillin, during the ongoing operative procedure.

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Table 1. Performance of Xpert MRSA/SA SSTI.

	Culture					
Xpert MRSA/SA SSTI		MRSA	MSSA	MR CoNS	Other Bacteria*	Sterile
	MRSA	4	-	-	-	-
	MSSA	-	7	-	-	-
	MR CoNS	-	-	14	-	-
	Negative	-	-	2	9	33+1**

*MS CoNS in 3 cases, *Streptococcus agalactiae* in 2 cases and *Streptococcus gordonii*, *E.aerogenes, E.faecal*is, and *Pseudomonas aeruginosa* in 1 case each

**1 case was confirmed to be PJI due to the presence of a fistula.

Table 2. Xpert performance in the present study and review of the literature.

	Study design	No. of patients	No. of GeneXpert positive for MRSA/PJI confirmed	GeneXpert performance for MRSA detection	No. of GeneXpert positive for MSSA/PJI confirmed	GeneXpert performance for MSSA detection	No. of GeneXpert positive for MR CoNS/PJI confirmed	GeneXpert performance for MR CoNS detection
Present study	Prospective	70			11/11	Sensitivity 100% Specificity 100%	14/16	Sensitivity 87% Specificity 100%
Valour et al. (2014)	Retrospective	76			68/72	Sensitivity 94,4% Specificity 100%		
Titecat et al. (2012)	Prospective	30			37/37	Sensitivity 100% Specificity 91.2%	12/13	Sensitivity 92%
Duboix-Bourandy et al. (2011)	Retrospective	105	2/2	Sensitivity 100% Specificity 100%	16/16	Sensitivity 100% Specificity 98.3%	23/23	Sensitivity 100% Specificity 95.3%
Lourtet-Hascoett et al. (2015)	Retrospective	62					9/16	Sensitivity 56%

Figure 1. Algorithm tree showing possible advantages of the use of Xpert MRSA/SA SSTI assay for a more rapid onset of target antibiotic therapy.