Rapid detection of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in nose, groin, and axilla swabs by the BD GeneOhm MRSA achromopeptidase assay and comparison with culture

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ABSTRACT

الأهداف: مقارنة كشف البكتيريا العنقودية المقاومة للمثيسلين MRSA على جهاز BD GeneOhm MRSA Achromopeptidase (ACP) assay وطريقة الزراعة للبكتيريا (أجار الدم و المانيتول).

الطريقة: أجريت هذه الدراسة على عينات عدد 102 مريض من مرضى وحدة العناية المركزة في مستشفى الملك خالد الجامعي خلال الفترة من يوليو 2010م حتى فبراير 2011م. وذلك بآخذ مسحات من الأنف و الإبط و الأربية الفخذية لكل مريض على جهاز BD GeneOhm MRSA Achromopeptidase (ACP) assay وطريقة الزراعة للبكتيريا (أجار الدم و المانيتول).

النتائج: كانت 21.6% من عينات المرضى ايجابية لهذه الجرثومة بواسطة طريقة MRSA–PCR و9% من العينات ايجابية بطريقة الزراعة. أما الحساسية لهذه الطريقة فكانت 88.4% و القيمة التنبؤية السلبية لطريقة MRSA–PCR فهي 98.6%. MRSA– PCR أعطت تقريباً نفس النتائج للجرثومة لمسحات الأنف و الاربية. MRSA–PCR أعطى نتائج ايجابية في 22.5% من المرضى من خلال عينات الأنف 27.5% من عينات المرضى من خلال الأنف، الفخذ. 30.4% من المرضى من خلال الأنف والإبط والفخذ. كما أن 30.4% هي نسبة النتائج الايجابية للمرضى الذين فحصت عيناتهم بطريقة MRSA–PCR بينما طريقة الزراعة كانت إيجابية للجرثومة بنسبة 19.6%من المرضى.

خاتمة: أن MRSA–PCR لها حساسية عالية وقيمة التخمين سلبية وتعد طريقة مفيدة لفحص المرضى لاستبعاد المرضى الذين لم يصابوا بالبكتيريا العنقودية المقاومة للمثيسلين.

Objectives: To compare the BD GeneOhm *Methicillin Resistant Staphylococcus aureus* (MRSA) Achromopeptidase (ACP) polymerase chain reaction (PCR) assay with the culture method for the detection of MRSA colonization.

Methods: One hundred and two patients were admitted to the Intensive Care Unit in King Khalid Hospital, Najran, Kingdom of Saudi Arabia from July 2010 to February 2011. Separate swabs from the nose, axilla, and groin of each patient were processed by the culture method (sheep blood agar plate and mannitol salt agar plate) and BD GeneOhm MRSA ACP assay.

Results: Of the 287 samples, 62 (21.6%) were MRSA positive by the PCR assay and 26 (9%) were MRSA positive by the culture method. The PCR method showed 88.4% sensitivity and 98.6% negative predictive value. The number of MRSA-PCR positive groin specimens was nearly the same as nasal specimens. The PCR method gave positive results in 22.5% of patients by nasal specimens, 27.5% of patients by nasal and groin specimens, and 30.4% of patients by nasal, groin, and axilla specimens. The PCR method detected 30.4% of patients as MRSA positive while the culture method detected 19.6% of patients as positive for MRSA.

Conclusions: The BD GeneOhm MRSA ACP assay has high sensitivity and NPV and hence is a useful screening method to exclude patients who are not colonized with MRSA.

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Beginning from the late 1970s and early 1980s and continuing to this day, there has been a growing incidence of hospital-acquired (nosocomial) and community acquired infections caused by strains of *Staphylococcus aureus* (*S. aureus)* that are resistant to multiple antimicrobials. Foremost among these strains are Methicillin-Resistant *S. aureus* (MRSA), which has gained worldwide notoriety as a hospital "superbug." Apart from methicillin, MRSA is resistant to as many as 20 different antimicrobial agents, representing most of the available drug classes.[1] Methicillin resistance in *S. aureus* is caused by acquisition of an exogenous gene, *mecA*, that encodes an additional β-lactam-resistant penicillin-binding protein (PBP) called PBP 2a (or PBP2').[2] The *mecA* gene is carried by a mobile genetic element, designated Staphylococcal cassette chromosome *mec* (SCC*mec*), inserted near the chromosomal origin of replication.[3] At least 7 SCC*mec* types (types I to VII) and several subtypes (especially of type IV), have been described.[4,5] A wide spectrum of infections, including skin and soft tissue infections, pneumonia, bacteremia, surgical site infections, and catheter-related infections are caused by MRSA. Infections by MRSA result in increased lengths of hospital stay, health care costs, morbidity, and mortality when compared to those caused by methicillin-sensitive *S. aureus* strains.[6] Screening every patient at the time of admission in the hospital for MRSA is an important "search and destroy" infection control policy. Infection control measures, including patient screening for MRSA colonization, cohorting and isolation of infected and colonized patients, decolonization procedures, and increased emphasis on appropriate hand-hygiene and use of appropriate personal protective equipments have reduced the clinical MRSA disease burden.[7] Intensive care unit admission of a patient with MRSA colonization is considered as a source of subsequent infection to other patients in the unit. If patients are not identified as MRSA positive on admission, the MRSA patients may remain as hidden reservoirs for cross-transmission until they are identified by regular culture methods. Culture-based detection of MRSA with traditional media requires 48-96 hours for results.[8,9] In contrast, the BD GeneOhm MRSA ACP real-time polymerase chain reaction (PCR) assay, formerly called the IDI-MRSA assay (BD diagnostics, San Diego, CA) offers rapid identification of MRSA-colonized patients, in as little as 2 hours.[10,11] The BD GeneOhm MRSA ACP assay is currently approved by the United States Food and Drug Administration (FDA) for detection of MRSA from nasal swabs. Many authors have used this assay for detecting MRSA from samples from other sites such as axilla, groin, throat, and rectum.[12-18] The real-time BD GeneOhm MRSA ACP assay is based on the primers developed by Huletsky et al.[19] The forward primers bind to the J3 region of the Staphylococcal cassette chromosome *mec* (SCC*mec*) and the reverse primer binds in the *orfX* region that is specific for *S. aureus.* The objective of the present study is to compare the BD GeneOhm MRSA ACP assay with culture method with respect to identification of patients with MRSA colonization in nose, axilla, and groin at the time of admission into the intensive care unit in King Khalid hospital, Najran.

Methods. This work has been approved by the Ethical Committee, King Khalid Hospital, Najran, Kingdom of Saudi Arabia. Medical and surgical patients for admission into the Intensive Care Unit from the Emergency room dating from July 2010 to February 2011 were screened for MRSA colonization by swabbing with separate dry, sterile swabs from the nose, groin, and axilla. The swabs were immediately transported to the laboratory, processed immediately or kept at +4^{0}C to +8^{0}C and processed within 24 hours after collection. Each swab was processed separately. The swabs were first inoculated onto a sheep blood agar plate and mannitol salt agar plate (Oxoid, Hampshire, UK). Then, the swab was placed in the sample buffer tube of the BD GeneOhm MRSA ACP assay kit and processed for PCR. The agar plates were incubated aerobically at 37^{o}C for 24-48 hours and the hemolytic colonies on the blood agar plates or yellow colonies on the mannitol salt agar plates were purified by sub-culturing onto another sheep blood agar plate. The subcultured colonies on sheep blood agar plates were checked for MRSA by standard procedures [Gram stain; 3% catalase; tube coagulase test (Coagulase plasma EDTA Selectavial- Code SV78 supplied by MAST DIAGNOSTICS, Merseyside, UK). To check for methicillin resistance, the growth was inoculated on Mueller Hinton agar plate and 4 μg oxacillin disc was placed; the plate was incubated aerobically at 37^{0}C overnight and the isolate was considered as MRSA if it was resistant to oxacillin.][20] The BD GeneOhm MRSA ACP assay was performed as per the manufacturer's instruction. The swab was placed briefly in the sample buffer tube, vortexed and the fluid was transferred to another tube containing the lysis buffer. The lysis tube was incubated at 37±2^{o}C for 20 minutes and then at 99±2^{o}C for 5 minutes, then the lysis tube was transferred to a cooling block. The lysate was transferred to a SmartCycler reaction tube containing the master

mix reagents. The reaction tube was placed in the SmartCycler (thermal cycler) instrument (CEPHEID, Sunnyvale, CA, USA) and the run was started. Positive and negative controls supplied along with the kit were included in each run and when both the controls were valid the run was considered as valid. The result for the sample is displayed as positive or negative or unresolved (if the internal control in a sample tube fails).

The overall agreement, sensitivity, specificity, confidence interval (CI), positive predictive value (PPV), and negative predictive value (NPV), were calculated by analyzing the data using SPSS 10 for Windows (SPSS Inc, New York,USA).

Results. Out of 306 samples from 102 patients, 19 (6.2%) samples were reported as unresolved by the PCR assay as the internal controls failed. These 19 samples were rerun as per the BD GeneOhm MRSA ACP assay manufacturer's instructions and were found to be unresolved. These 19 unresolved samples were excluded from the analysis and 287 samples were included for final analysis. Criteria used in the comparison of the 2 methods: a true-positive sample is one, which is positive by both PCR and culture methods; a true-negative result is negative by both methods; a sample which is positive by PCR, but negative by culture is considered as false-positive by PCR method; a sample which is negative by PCR, but positive by culture is considered as false-negative by PCR method. The results from the BD GeneOhm MRSA ACP assay and the results of the culture method for the detection of MRSA from 287 nose, groin, and axilla samples are given in **Table 1**. Of the 287 samples, 62 (21.6%) were MRSA positive by the PCR assay and 26 (9%) were MRSA positive by the culture method. Out of 287 samples, 222 (77.4%) samples were MRSA negative by both methods (true negative), 23 (8%) were MRSA positive by both methods (true-positive), 3 (1.1%) samples (groin and nose from one patient and axilla from another patient) were culture positive but negative by the PCR method (false-negative), and 39 (13.6%) were MRSA positive by the PCR method but negative by the culture method (false-positive). The overall agreement of both methods was 85.4% (245/287). Compared to the culture method, the PCR method showed 88.4% sensitivity, 85% specificity, 98.6% NPV, and 37.1% PPV for the samples from nose, axilla, and groin together. The

Table 1 - Comparison of BD GeneOhm Methicillin Resistant *Staphylococcus aureus* (MRSA) Achromopeptidase (ACP) assay with the culture method for the detection of MRSA from nose, groin, and axilla swabs.

BD GeneOhm MRSA ACP assay	Culture for MRSA			% Sensitivity (95% CI)	% Specificity (95% CI)	%NPV (95% CI)	%PPV (95% CI)
	Number positive	Number negative	Total				
Nasal swabs							
Number positive	14	9	23	93.3 (66-99)	88.1 (78.2-94.1)	98.5 (91-99.9)	60.8 (38.7-79.5)
Number negative	1	67	68				
Total	**15**	**76**	**91**				
Groin swabs							
Number positive	7	18	25	87.5 (46.6-99.3)	79.5 (69.3-87.1)	98.5 (91.3-99.9)	28 (12.8-49.5)
Number negative	1	70	71				
Total	**8**	**88**	**96**				
Axilla swabs							
Number positive	2	12	14	66.6 (12.5-98.2)	87.6 (79-93.1)	98.8 (92.7-99.9)	14.2 (2.5-43.8)
Number negative	1	85	86				
Total	**3**	**97**	**100**				
Nose, axilla, and groin swabs together							
Number positive	23	39	62	88.4 (68.7-96.9)	85 (80-89)	98.6 (95.8-99.6)	37.1 (25.4-50.3)
Number negative	3	222	225				
Total	**26**	**261**	**287***				
MRSA colonized patients							
Number positive	19	12	31	95 (73-99)	85.3 (75.4-91.8)	98.5 (91.3-99.9)	61.2 (42.3-77.6)
Number negative	1	70	71				
Total	**20**	**82**	**102**				

CI - confidence interval, NPV - negative predictive value, PPV - positive predictive value.
*Out of 306 samples, 19 samples were reported to be "unresolved" by the BD GeneOhm MRSA ACP assay. Therefore these 19 samples were not included in the statistical analysis and only 287 samples were analyzed.

Table 2 - Numbers of Methicillin Resistant *Staphylococcus aureus* (MRSA) positive (+) specimens from one site, but negative (-) from another site in the same patient taken at the same time were analyzed by the BD GeneOhm MRSA Achromopeptidase (ACP) assay and the culture methods.

Methods	Nose + Groin -	Nose + Axilla -	Groin + Nose -	Groin + Axilla -	Axilla + Nose -	Axilla + Groin –
GeneOhm MRSA ACP assay	3	11	5	12	4	3
Culture	10	13	5	6	3	3

comparison of the BD GeneOhm MRSA-PCR assay with the culture method in samples from the nose, axilla, and groin, separately is shown in **Table 1**. The MRSA PCR assay was positive in 23/91 (25.3%) samples from the nose, 25/96 (26%) samples from the groin, and 14/100 (14%) samples from the axilla. The culture method was positive for MRSA in 15/91 (16.5%) samples from the nose, 8/96 (8.3%) samples from the groin, and 3/100 (3%) samples from the axilla. Compared to the culture method, the PCR method showed 93.3% sensitivity, 88.1% specificity, 98.5% NPV, and 60.8% PPV for the nasal samples. Compared to the culture method, the PCR method showed 87.5% sensitivity, 79.5% specificity, 98.5% NPV, and 28% PPV for the groin samples. Compared to the culture method, the PCR method showed 66.6% sensitivity, 87.6% specificity, 98.8% NPV, and 14.2% PPV for the axilla samples. However, the 95% confidence intervels, especially for sensitivity, are very wide reflecting the low precision due to the small sample size. The number of MRSA-colonized patients (determined as having any of the 3 samples collected as positive) was analyzed (**Table 1**). Out of the 102 patients, the culture method detected 20 (19.6%)patients as MRSA positive and the PCR method detected 31 (30.4%) patients as MRSA positive. In 19/102 (18.6%) patients MRSA was detected by both methods. In 12/102 (11.8%) patients the PCR method was positive but the culture method was negative for MRSA. Out of the 102 patients one (0.9%) was positive for MRSA by the culture method and negative by the PCR method. Both methods were negative for MRSA in 70/102 (68.6%) patients. The overall agreement between both methods was 87.2% (89/102). Compared to the culture method the PCR method showed 95% sensitivity, 85.3% specificity, 98.5% NPV, and 61.2% PPV. The number of MRSA positive samples from one site, but negative from another site of the same patient taken at the same time is shown in **Table 2**. Five groin samples were MRSA positive by the PCR assay, while nasal samples from the same patients were MRSA-PCR negative. Using MRSA-PCR assay 4 axilla samples were MRSA positive but the same patients had MRSA negative nasal samples.

Discussion. In our study, the BD GeneOhm MRSA-PCR assay provided positive results in 21.6% of specimens whereas the culture method was positive in 9% of specimens only (nose, groin, and axilla together). Compared to the culture method the MRSA-PCR assay had 88.4% sensitivity and 98.6% NPV for samples taken from all 3 sites together. The sensitivity and NPV of the MRSA-PCR assay were 93.3% and 98.5% for nasal samples, 87.5% and 98.5% for groin samples, and 66.6% and 98.8% for axilla samples, respectively. Earlier studies have reported 88.5% to 100% sensitivity and 97.9% to 100% NPV of the MRSA-PCR method when compared to the culture method.[11,17,21-24] Bishop et al[17] have reported that IDI-MRSA showed 83.3% sensitivity and 98.1% NPV for groin samples. The high NPV of MRSA-PCR assay in our study and other studies suggests that the MRSA-PCR assay provides a rapid method for the identification of persons who are not colonized with MRSA and in this context is likely to be useful for epidemiologic or surveillance activities. The BD GeneOhm MRSA assay showed 85% specificity and 37.1% PPV for nose, groin, and axilla samples together. The specificity and PPV of MRSA-PCR assay were 88.1% and 60.8% for nasal swabs, 79.5% and 28% for groin swabs and 87.6% and 14.2% for axilla swabs, respectively. Earlier studies for nasal samples have reported 90.4% to 98.6% specificity and 56.3% to 95.8% PPV by MRSA-PCR method when compared to culture method.[11,17,21-24] Bishop et al[17] have reported that IDI-MRSA-PCR assay showed 90.2% specificity and 46.9% PPV for groin samples. Although MRSA can be found in many body sites, such as the throat, groin, gastrointestinal tract, and wounds,[13,25-28] the most common site for MRSA carriage is the nose. The BD GeneOhm MRSA ACP assay is intended for use with swabs from the nose. Checking sites other than the nose (such as the axilla and groin) will increase the sensitivity of detection of MRSA, as MRSA is present in these areas as well. Earlier studies have reported the detection of MRSA from sites other than the nose by the BD GeneOhm MRSA ACP assay.[12-18] In our study, the MRSA-PCR positivity percentage of the groin samples was the same as that of the nasal samples (26% versus

25.3%). The sensitivity and NPV of the MRSA-PCR assay from the groin samples (87.5% and 98.5%) were almost similar to those of the nasal samples (93.3% and 98.5%) suggesting that groin swabs are suitable specimens for MRSA-PCR assay. A similar view had been expressed by Lucke et al.[12] In our study, the MRSA-PCR assay was positive in the groin swabs of 5 patients, while swabs from the nose of the same patients were negative. The MRSA-PCR assay was positive in the axilla swabs of 4 patients, while swabs from the nose of these patients were negative by the MRSA-PCR assay. The MRSA-PCR assay was positive in the axilla swabs of 3 patients, while swabs from the groin of these patients were negative by the MRSA-PCR assay. Therefore, performing the MRSA PCR assay from 3 sites (nose, groin, and axilla) from one patient will detect more number of MRSA colonized patients when compared to the performance of a single nasal swab for MRSA PCR from one patient. Bishop et al[17] also have reported that MRSA was positive in 5 groin samples, whereas nasal samples from the same patients were negative for MRSA by IDI-MRSA assay. Hombach et al have reported that the GeneOhm MRSA assay detected 4/16 MRSA carriers by nose alone, 4/16 by groin alone and 8/16 by both nose and groin specimens.[18]

In our study, the MRSA-PCR assay detected a large number of MRSA colonized patients than was detected by the culture method (30.4% and 19.6% patients, respectively). Nasal samples alone detected 23/102 (22.5%) patients as MRSA positive by the MRSA-PCR assay. Nasal and groin samples together detected 28/102 (27.5%) patients as MRSA positive by the MRSA-PCR assay. Axilla, groin and nasal samples together detected 31/102 (30.4%) patients as MRSA positive by the MRSA-PCR assay. Therefore, in order to detect all or most of the MRSA positive patients, it is better to collect samples from the nose, groin, and axilla from each patient and perform the MRSA-PCR assay rather than collecting a single nasal sample. However, screening 3 sites (nose, groin, and axilla) from each patient by 3 MRSA-PCR tests will increase the cost of the assay. Bishop et al[17] have reported that the IDI-MRSA assay of a single combined nose-groin specimen appears to have accuracy similar to those of separate nose and groin PCR assays and this approach is likely to result in cost savings. Svent-Kucina et al[15] have used pooled samples from the nose, skin, with or without the throat for MRSA detection by the GeneOhm MRSA assay and reported that it was a cost-effective way of screening for MRSA.

However, there are instances, wherein the MRSA PCR assay gave false positive results when tested with coagulase negative Staphylococcal culture isolates or *Methicillin-Sensitive Staphylococcus aureus* (MSSA) culture isolates. Malhotra-Kumar et al[29] have reported that the BD GeneOhm MRSA assay gave false positive results with select coagulase-negative Staphylococci. Bartels et al[30] have reported that 8/53 (15%) MSSA isolates gave false-positive results by the GeneOhm MRSA assay.[30] False positives that occur with methicillin sensitive *S. aureus* are most likely to result from the absence of the *mecA* gene in strains that have retained a residual SCC*mec* right-extremity fragment that is amplified by this method.[19] Desjardins et al[31] and Paule et al[32] have reported relatively high frequencies of false positive results by the MRSA-PCR assay. In our study, there was 1/102 (1%) patient who was culture positive (groin and nasal swabs), but MRSA-PCR negative. Such false-negative MRSA-PCR results may be due to low numbers of MRSA in the swabs namely, below the detection limit of the assay.[33] Bartels et al[30] found that 54/349 (15.5%) MRSA isolates from Denmark were false negative by the GeneOhm MRSA PCR assay. These authors have stated that the BD GeneOhm MRSA assay lack sensitivity in detecting isolates of SCC*mec* type IVa and have suggested that the BD GeneOhm MRSA assay be evaluated against the local MRSA diversity before being established as a standard assay.

A major difficulty in evaluating molecular assays for the detection of MRSA from clinical specimens is defining true-positive and true-negative specimens. Generally, the MRSA culture method is considered as a gold standard for comparison of the MRSA-PCR assay, as the culture is the only method in use for long period of time and any new method has to be compared with the earlier known culture method. In this approach, a MRSA-PCR positive but culture-negative result from a sample is considered as a false-positive result by PCR. This approach has the following disadvantages. 1) Different culture media used for the isolation of MRSA have been known to have limitations in sensitivity and Paule et al[32] have suggested that agar-based surveillance remains less sensitive than molecular amplification even when broth enrichment is included. 2) Earlier studies have reported that a culture negative, but PCR positive samples had been shown to grow MRSA in an additional broth enrichment procedure and the broth enrichment procedure had an advantage of increasing the sensitivity of detection of MRSA.[33] Nahimana et al have found a sensitivity of 47-65% with direct plating to 4 chromogenic medium products to 79-95% when prior broth enrichment was included.[8] 3) Some of the patients with such false-positive PCR results were found to have a past

history of MRSA infection/colonization.[21] Paule et al[32] have opined that such samples can be calculated as "false-positive PCR result" or "potentially false-negative cultures." Lucke et al[12] have considered PCR-positive and culture-negative results as true positive, if there were PCR-positive and culture-positive results from other body sites of the same patient at the same time. Similar approach of revised or amended calculations had been used by de San et al.[21] Positive PCR results always need confirmation with culture in order to exclude false-positive results or to use the isolates for further testing such as for antimicrobial susceptibility. Nour de San et al[21] and Enno Sturenburg[34] have suggested to perform both the culture method and the MRSA-PCR assay to screen MRSA from clinical specimens.

The conclusions from this study are: the BD GeneOhm MRSA ACP assay has high sensitivity and NPV and hence is a useful screening method to exclude patients who are not colonized with MRSA. However, the present study has a limitation of small sample size, as reflected in the wide 95% confidence interval for sensitivity. The number of MRSA-PCR positive groin specimens was nearly same as MRSA positive nasal specimens. To detect all or most of the MRSA positive patients, it would better to collect samples from three sites (nose, groin, and axilla) and perform a MRSA-PCR assay rather than analyzing a single nasal sample. To reduce the cost from three MRSA PCR assays for one patient , further investigations are needed to perform a single MRSA PCR assay after combining the three swabs into a single MRSA PCR assay.

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