Rapid Screening for Carriage of Methicillin-Resistant Staphylococcus aureus by PCR and Associated Costs

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PCR tests for the rapid and valid detection of methicillin-resistant Staphylococcus aureus (MRSA) are now available. We evaluated the costs associated with contact screening for MRSA carriage in a tertiary-care hospital with low MRSA endemicity. Between 1 October 2005 and 28 February 2006, 232 patients were screened during 258 screening episodes (644 samples) for MRSA carriage by GenoType MRSA Direct (Hain Lifescience GmbH, Nehren, Germany). Conventional culture confirmed all PCR results. According to in-house algorithms, 34 of 258 screening episodes (14.7%) would have qualified for preemptive contact isolation, but such isolation was not done upon negative PCR results. MRSA carriage was detected in 4 (1.5%) of 258 screening episodes (i.e., in four patients), of which none qualified for preemptive contact isolation. The use of PCR for all 258 screening episodes added costs (in Swiss francs [CHF]) of CHF 104,328.00 and saved CHF 38,528.00 (for preemptive isolation). The restriction of PCR screening to the 34 episodes that qualified for preemptive contact isolation and screening all others by culture would have lowered costs for PCR to only CHF 11,988.00, a savings of CHF 38,528.00. Therefore, PCR tests are valuable for the rapid detection of MRSA carriers, but high costs require the careful evaluation of their use. In patient populations with low MRSA endemicity, the broad use of PCR probably is not cost-effective.

Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most important nosocomial pathogens worldwide, and it causes significant morbidity and mortality (1, 9, 13). Once colonized with MRSA, 11 to 25% of patients in acute-care facilities and 3 to 15% in chronic-care facilities subsequently will develop infection (4, 17, 20, 21). Infection control programs can reduce the nosocomial MRSA transmission rate to at least two-thirds of its baseline level and have been proven to be cost-effective (3, 5, 11). Screening for MRSA is a key component of successful infection control strategies (3), since they identify hidden reservoirs of MRSA transmission and allow for interrupting such transmission chains.

Conventional culture-based detection methods for MRSA are time-consuming, which leads to delayed or unnecessary isolation precautions. Recently, rapid detection assays for MRSA have been developed. Real-time PCR for the simultaneous detection of the mecA gene and species confirmation by an S. aureus-specific genomic fragment offer fast results with good sensitivity, but they are limited by the inability to distinguish coagulase-negative Staphylococcus species in mixed specimens such as screening swabs (10, 18, 24). IDI-MRSA (Infectio Diagnostic, Québec, Canada) and GenoType MRSA Direct (Hain Lifescience GmbH, Nehren, Germany) are real-time, conventional PCR methods that target sequences within the SCCmec (IDI-MRSA), the mobile genetic element harboring the mecA gene, and orfX, a highly conserved open reading frame in S. aureus that represents the site of SCCmec integration into the genome (GenoType MRSA Direct). Both tests can detect MRSA within a few hours directly from screening swabs with good sensitivity and excellent specificity of 81 to 92% and 93 to 98%, respectively (2, 8, 15, 16, 22, 25). In a mathematical model, the rapid detection of MRSA carriers was an important parameter for MRSA control (3). However, PCR tests are still costly and may not be available (on a large scale). In addition, the logistics of sampling patients in a timely manner for rapid PCR are demanding. Therefore, the optimal use of rapid PCR screening needs to be determined.

The aim of this study was to evaluate the use of a commercial MRSA PCR test for contact screening in a tertiary-care university hospital with low MRSA endemicity (MRSA rate of <5% of the clinical S. aureus isolates) (20).

(Part of these data were presented at the Annual Assembly of the Swiss Society for Infectious Diseases, Zürich, Switzerland, 14 to 15 June 2007 [poster no. 175].)

MATERIALS AND METHODS

Study setting and patients. The study was performed according to local ethical standards. The University Hospital of Berne is a tertiary-care center with approximately 1,000 beds and more than 30,000 admissions per year. During the past 10 years, the local level of MRSA endemicity remained low (<5%). This study was performed between 1 October 2005 and 28 February 2006. During this time period, according to routine local policies 232 patients were screened for MRSA carriage caused by recent contact (i.e., in the same room or same ward) with a newly detected MRSA carrier and upon admission and after being transferred from an MRSA high-risk area. Follow-up screening cultures of known MRSA carriers were excluded from the analysis. Screening samples included routine swabs (Venturi Transystem, Copan Italia Spa, Brescia, Italy) of the following anatomical sites in all patients: both nares (with one swab) and both groins (with one swab). Additional swabs or samples were taken depending on the clinical conditions from any skin lesions, tracheal secretions in intubated or
tracheostomized patients, and urine in patients with urinary catheters. Urine was collected into commercial tubes containing boric acid (BD Vacutainer and C&S boric acid kit; BD Diagnostics, Franklin Lake, NJ).

**Culture and PCR for detection of MRSA.** MRSA detection was performed by manual culture and PCR as previously reported (7 and K. Bögli-Stuber, K. Mühlmann, T. Bodmer, and S. Droz, poster C-065, 106th General Meeting of the American Society for Microbiology). The sensitivity and specificity of the PCR assay GenoType MRSA Direct were evaluated in our patient population on a total of 1,488 screening samples collected between 2005 and 2006 and were found to be 92.6 and 98.9%, respectively, with a negative predictive value of 99.9% and a positive predictive value of 61% (K. Bögli-Stuber et al., poster C-065, 106th General Meeting of the American Society for Microbiology). PCR was not done for urine, since the test had not been validated for urine samples. Collected specimens were transported and stored at room temperature and processed within 24 to 48 h after being collected. After the processing of the swab for GenoType MRSA Direct, first the biplate and then the enrichment broth were inoculated with the same swab.

For local logistical reasons, PCR testing on the day of screening (designated Fast PCR) could be done only on working days and only for patients that qualified for preemptive contact isolation (see below). For all of the other patients and on weekends, PCR results were available within 24 to 48 h. PCR results were communicated promptly to the infection control team by phone or fax.

**Selective media and culture conditions.** Enrichment broth, containing nutrient broth no. 2 (Oxoid, United Kingdom) and 6% sodium chloride, and a 4% biplate, consisting of mannitol salt agar (Oxoid) and oxacillin screen agar and containing 6 µg of oxacillin per ml (BioMérieux), were used as selective media. Biplates were incubated for 48 h at 35°C. Enrichment broths were incubated at 35°C for 18 to 24 h and then were subcultured onto fresh biplates. Biplates were read after 24 and 48 h. Identification was performed according to the standard laboratory protocol.

GenoType MRSA Direct was done according to the manufacturer’s description. After washing out the swabs in 300 µl lysis buffer, samples were incubated at 95°C for 10 min in a heating block, followed by centrifugation at 10,900 × g for 5 min. The supernatant was transferred to a new tube, and PCR was performed by using a GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA) with a Gold Block and maximum ramp speed. The 50-µl reaction mix contained 35 µl primer nucleotide mix (provided by the kit), 1× PCR buffer (Qiagen, Basel, Switzerland), 1 mM MgCl2 (Qiagen, Basel, Switzerland), 1.25 U of HotStarTaq polymerase (Qiagen, Basel, Switzerland), and approximately 10 ng of DNA (5 µl). The PCR conditions were 5 min at 95°C followed by 35 cycles of 95°C for 1 min, 55°C for 40 s, and 72°C for 40 s.

**Isolation precautions.** Isolation precautions during this study were performed according to routine local policies. Preemptive isolation precautions were not started for all patients with an indication for MRSA screening but for a subset of screened patients who (i) shared a room with a newly detected MRSA carrier or (ii) were transferred from another geographical region with high MRSA prevalence and the presence of any risk factor for MRSA colonization, including skin lesions, intratracheal tube, tracheostoma, urinary catheter, or wound drainage. For all other patients who had an indication for MRSA screening (as described above), isolation was started only in the case of a positive MRSA screening test (PCR and/or culture). Contact precautions included a single patient room, the use of gloves and gowns by medical staff during physical contact, and surgical masks if exposure to respiratory secretion was to be expected. Preemptive contact isolation was stopped if (i) PCR results were negative or (ii) culture results were negative following a positive PCR result. Patients that qualified for preemptive isolation and who were screened by PCR on the same day were not isolated and remained in the same patient room while waiting for the test result. However, if same-day testing was not possible (e.g., on weekends), they were isolated until screening results became available (after 24 to 48 h or longer).

**Calculation of costs.** All costs are calculated in Swiss francs (CHF; at the time of writing, CHF 1.00 corresponds to 0.61 euros and $0.82). Extra costs of CHF 301.00 per patient day were calculated for the use of a single room for all patients without private insurance. Expenses for isolation material (e.g., gowns and gloves) and extra staff time were not counted. The cost per PCR was CHF 162.00, and costs for negative and positive MRSA cultures were CHF 28.35 and 64.80, respectively. Costs for urine cultures were not included in the cost analysis, since urine samples were not tested by PCR (see above). Based on local experience, the time interval from the availability of the Fast PCR and culture results was assumed to be 4 days.

**RESULTS**

During the 4-month study period, a total of 647 screening samples, corresponding to 258 screening episodes for 232 patients, were analyzed. Three (0.5%) samples were excluded from the analysis due to inhibition during PCR. Fast PCR was done for 34 (13.2%) screening episodes (74 samples) that qualified for preemptive contact isolation, none of which gave a positive result (Fig. 1). The remaining 224 (86.8%) screening episodes (570 samples) were tested within 24 to 48 h. MRSA was detected in four patients, i.e., in 4 (1.6%) of the 224 screening episodes. Eight screening samples had been obtained from these four MRSA carriers. Five (three nasal swabs and two groin swabs) were positive by PCR and by culture. One groin swab was positive by PCR and negative by culture, but the nasal swab from the same patient was positive by culture and by PCR. Otherwise, there were no discrepancies between PCR and culture results, and none of the screenings yielded MRSA by urine culture only. MRSA cultures in the four newly detected MRSA carriers took 3 days (one patient), 4 days (two patients), or 6 days (one patient) from sample collection to detection. PCR results were available within 24 h. None of the four MRSA carriers qualified for preemptive contact isolation. They exposed 19 other patients, of which 4 qualified for preemptive contact isolation. MRSA screenings were done by PCR and culture on the 19 contact patients, and none was MRSA positive (those patients were not part of the 258 cases included in the study).

The costs associated with MRSA screening were influenced mainly by the algorithms employed for the use of direct PCR and the preemptive isolation of screened patients until the results of screening were available (Table 1). Direct PCR incurred extra costs in our setting, with the use of PCR on all screened patients and the restriction of preemptive isolation to a selected patient group. Direct PCR would have lowered costs by CHF 166,633.00 (the calculation for the preemptive isolation is not shown) if the indication for preemptive isolation could have been extended to all 232 screened patients, i.e., all 258 screening episodes. In this setting, PCR would have been cost saving (CHF 56,146.00). Cost saving (CHF 24,920.00) also was reached when direct PCR was restricted to the selected
patient group that qualified for preemptive contact isolation (Table 1).

**DISCUSSION**

The rapid detection of MRSA carriers is a key parameter for MRSA control (3). PCR assays are now available that offer rapid, sensitive, and specific MRSA detection directly from patients’ samples (2, 8, 15, 16, 22, 25, and K. Bölgi-Stubber et al., poster C-065, 106th General Meeting of the American Society for Microbiology). However, the broad use of MRSA PCR assays is hampered by high costs for PCR (19), the limited capacity of laboratories to turn around a large number of samples in a short time, and the logistics associated with sampling patients in a timely manner for rapid PCR. Therefore, the optimal use of rapid PCR screening needs to be evaluated. Our study demonstrates that screening with the GenoType MRSA Direct gives rapid and valid results, but the cost efficacy of the direct PCR depends on the local MRSA epidemiology and the local infection control algorithms employed.

If PCR was used for all patients included in contact screenings, costs were considerably higher than those for conventional culture methods. Several factors play a role. First, costs for PCR assays were much higher than those for conventional culture (19, 23). However, in our setting, even a PCR assay at half the current price (i.e., CHF 81.00 instead of CHF 162.00 per test) would not have been cost saving. Second, cost savings depend on the number of preemptive isolation days that can be saved due to negative PCR results. The situation also may be different in settings with lower MRSA prevalence and transmission rates.

Preemptive isolation aims at the prevention of secondary MRSA cases while waiting for screening results. However, to our knowledge there are no data on the most efficient use of preemptive isolation. Our local algorithm was based on the assumption that preemptive isolation is of most benefit when applied to potential MRSA carriers who present with risk factors for MRSA colonization, such as skin lesions, wound drainage, and endotracheal intubation. In this study, no secondary MRSA cases were detected among those who came in contact with the four MRSA carriers who had not been under preemptive isolation and were found to be MRSA positive by PCR screening within 24 h after admission. However, we do not know if waiting for conventional culture results (an average of 3 to 4 days) would have led to secondary MRSA transmissions. The situation also may be different in settings with higher MRSA prevalence and transmission rates.

A second issue in this study was that PCR screening within 12 h had to be limited to the subset of patients who qualified for preemptive isolation. The remaining PCR results became available within 24 to 48 h, which is still below the average time required for conventional culture (3 to 4 days). As discussed above, there are no data available that demonstrate that a delay of 24 to 48 h has a significant impact on the risk of MRSA transmission. It is likely that the presence of risk factors for MRSA transmission in MRSA carriers and local hygiene standards play a role. Cunningham et al. demonstrated that MRSA screening by PCR on admission to an intensive care unit reduced nosocomial MRSA transmission (6). The study by Harbarth et al. could not show a consistent positive effect of rapid admission screening on the MRSA infection rate (14). Therefore, the rapid identification of MRSA carriers alone is no guarantee for MRSA control.

Our study has some limitations. Cost analysis was restricted to costs caused by MRSA detection tests and the use of a single-patient bedroom for preemptive isolation, but it did not include isolation costs due to additional staff and isolation material (gowns, gloves, etc.). Also, because of the low level of MRSA endemicity, the number of MRSA carriers detected by screening was small and secondary MRSA transmission was not observed. Optimally, cost calculations should consider the prevention of secondary MRSA carriers and MRSA infection. However, such costs are difficult to estimate (12). The results presented here may only in part be extrapolated to other institutions with different MRSA epidemiology and local resources, but they demonstrate the factors to consider when implementing rapid screening for MRSA carriers.

In summary, PCR tests are valuable for the rapid detection

**TABLE 1. Costs (in CHF) associated with MRSA screening by direct PCR according to three different algorithms**

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>No. of screening episodes for:</th>
<th>Cost of a:</th>
<th>Savings of contact isolation d</th>
<th>Total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCR Culture</td>
<td>PCR Culture</td>
<td>Secondary PCR e) (n = 19)</td>
<td>Secondary</td>
</tr>
<tr>
<td>PCR for selected patients  b)</td>
<td>34</td>
<td>258</td>
<td>11,988.00 18,476.00</td>
<td>1,620.00</td>
</tr>
<tr>
<td>PCR for all patients</td>
<td>258</td>
<td>258</td>
<td>104,328.00 18,476.00</td>
<td>6,156.00</td>
</tr>
<tr>
<td>No PCR</td>
<td>0</td>
<td>258</td>
<td>0.00</td>
<td>18,476.00</td>
</tr>
</tbody>
</table>

a) Selected patients included patients who shared a room with a newly detected MRSA carrier or who transferred from a geographical region with high MRSA prevalence and presented with risk factors for MRSA colonization, including skin lesions, intratracheal tube, tracheostoma, urinary catheter, or wound drainage.

b) The costs were the following: (i) CHF 301.00 per patient day of preemptive isolation in a single room for an average of 4 days for patients without private insurance, (ii) CHF 162.00 per PCR test, and (iii) CHF 28.35 and 64.80 for negative and positive MRSA cultures, respectively. At the time of writing, CHF 1.00 corresponds to 0.61 euros and $0.82.

c) Secondary costs refers to costs associated with the screening of patients who were in contact with any of the four MRSA carrier patients detected by screening. Of the 19 exposed patients, 4 qualified for preemptive contact isolation.

d) Thirty-two of 34 patients had no private insurance and would have been transferred to a single room.
of MRSA carriers, but high costs require the careful evaluation of their use. In patient populations with low MRSA endemicity, the broad use of PCR may not be cost-effective. Nevertheless, the rapid detection of MRSA carriers is important in institutions with low MRSA prevalence, since MRSA control is easiest when rates are still low, and maximal efforts should be made to maintain such epidemiology.

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REFERENCES


