Cost-benefit and Effectiveness Analysis of Rapid Testing for MRSA Carriage in a Hospital Setting

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ABSTRACT

A cost-effectiveness analysis was conducted comparing the polymerase chain reaction assay and traditional microbiological culture as screening tools for the identification of methicillin-resistant *Staphylococcus aureus* (MRSA) in patients admitted to the pediatric and surgical intensive care units (PICU and SICU) at a 722 bed academic medical center. In addition, the cost benefits of identification of colonized MRSA patients were determined. The cost-effectiveness analysis employed actual hospital and laboratory costs, not patient costs. The actual cost of the PCR assay was higher than the microbiological culture identification of MRSA ($602.95 versus $364.30 per positive carrier identified). However, this did not include the decreased turn-around time of PCR assays compared to traditional culture techniques. Patient costs were determined indirectly in the cost-benefit analysis of clinical outcome. There was a reduction in MRSA hospital-acquired infection (3.5 MRSA HAI/month without screening versus 0.6/month with screening by PCR). A cost-benefit analysis based on differences in length of stay suggests an associated savings in hospitalization costs: MRSA HAI with 29.5 day median LOS at $63,810 versus MRSA identified on admission with 6 day median LOS at $14,561, a difference of $49,249 per hospitalization. Although this pilot study was small and it is not possible to directly relate the cost-effectiveness and cost-benefit analysis due to confounding factors such as patient underlying morbidity and mortality, a reduction of 2.9 MRSA HAI/month associated with PCR screening suggests potential savings in hospitalization costs of $142,822 per month.

ABBREVIATIONS: MSSA - methicillin sensitive *Staphylococcus aureus*; MRSA - methicillin-resistant *Staphylococcus aureus*; PCR - polymerase chain reaction; HAI - hospital acquired infection; LOS - length of stay

INDEX TERMS: Methicillin resistant *Staphylococcus aureus*, infection control, cost-benefit analysis, polymerase chain reaction

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing problem in health care, worsening both morbidity and mortality in patient populations, as well as increasing health care costs.[1,2] Recently, there have been several initiatives aimed at decreasing the number

of MRSA infections in hospitalized patients. These included bundling of screening tests and preventive measures in various settings, notably in high-risk patients (surgical, critically ill), but also in general ward patients. Health interventions of any type are designed to include treatment, screening tests, or primary prevention techniques.[3-7] Similarly, formal involvement of the clinical laboratory should be included in any initiatives to increase microbe-specific surveillance in an institution.[5] As part of the planning and implementation phase of any microbial surveillance, several key factors must be addressed: ability and readiness of the laboratory personnel to handle the additional workload, potential reduction in turn-around time for screening tests, ability of infection prevention staff to monitor screening results, education of hospital staff, and collection of outcomes data for evaluation of the program.[6] Given the current state of limited resources, it is critical that the most economical and effective measures be used.[8]

Polymerase chain reaction (PCR) has been used in the clinical laboratory for many years. Recently, platforms like the Cepheid GeneXpert® have been introduced to the lab. These systems provide an all-inclusive testing apparatus with rapid turn-around times. Cost is often one of the major hindrances for institutions considering their use. However, the role of PCR-based screening assays in facilitating real-time infection prevention intervention may provide some balance to the cost argument. The aim of this study was two-fold. First, a cost-effectiveness analysis was performed for rapid detection of MRSA using PCR technology combined with an intervention strategy. For the cost-effectiveness analysis, laboratory and hospital costs were employed from the institution. Secondly, a cost-benefit analysis of hospitalization costs (patient costs) were estimated by comparing interventions designed to minimize infections. Using these we compared traditional microbiological cultures and PCR as screening methods, including the cost of preventive measures in the case of MRSA-positive screening results. Data is also presented for the cost of treatment for infection.

METHODS

A cost-effectiveness analysis was developed using an outcomes tree which includes the following parameters: (1) no screening program, (2) screening all patients on admission with traditional microbiological techniques, and (3) screening all patients on admission with PCR technology. Each of these parameters subsequently gives rise to specific outcomes which can be included in a cost-effectiveness analysis. The three major outcomes are total direct medical costs, MRSA infection rate, and increased length of stay. Data for the cost of microbiological testing, including cost of reagents, technician time, and instrumentation, were obtained from the clinical laboratory based on actual costs incurred.

Based on the volume of tests done at the institution, a rate of approximately $2/agar plate was estimated. The cost of PCR screening for MRSA was based on the Cepheid GeneXpert® MRSA assay. The institutional cost for each GeneXpert® MRSA cassette was $36/test. Routine instrument maintenance and calibrations are included in a service contract with the manufacturer for $3000/month ($36,000/year). Quality controls used in accreditation are also performed with each new lot of reagents, or every 30 days, whichever comes first. Typically, 10-12 cassettes are used for these routine quality control procedures but the costs were not included in the analysis presented here. We examined admissions to the surgical intensive care unit (SICU), as well as the pediatric intensive care unit (PICU). Over a 3 month period of September-November 2011, the total number of patients screened as well as the number of positive (colonized) patients was recorded.

The numbers of methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA infections were determined by a review of patient discharge summaries during a 7 month period (January 1-July 31, 2011). Records were screened using International Classification of Diseases, Ninth Revision (ICD-9) codes for MRSA (041.12, V02.54) and MSSA (041.11, V02.53). This was performed as part of routine quality improvement/ infection prevention and was not subject to IRB approval. Patients with a prior MRSA infection or colonization noted in their medical record, either from the institution or from referring physicians/institutions, were considered MRSA-positive. These patients were not re-screened and were placed on contact isolation and cared for employing standard contact precautions.[9] A second group of patients, those being admitted to the selected acute care units (SICU and PICU), were screened for MRSA by PCR assay as part of a feasibility pilot program at the institution. Patients diagnosed with

MRSA 72 hours or more after hospital admission were determined to have MRSA hospital-acquired infection (HAI).[9] Patients were not routinely screened for MRSA by either culture or PCR assay prior to a pilot study included here. However, the institution has employed microbiological screening for MRSA with selective agar (BD CHROMagarMRSA™, BioRad MRSA Select™, bioMerieux chromID®MRSA) when required for standard care.

For evaluation of cost-minimization, an alternative model was developed. The cost of treatment for MRSA infection was based on both the actual cost of the antibiotic as well as the recommended length of treatment. The cost of specific antibiotics was obtained from the pharmacy. The total cost was estimated based on the current standard of care for patient groups requiring different hospital courses, i.e., general admission, surgical, and ICU patients. MRSA treatment often requires prolonged courses of intravenous antimicrobials. The treatment of choice remains vancomycin for the majority of patients given the low concentration of vancomycin-resistant MRSA, as well as its very low cost compared to other anti-MRSA agents.[10]

RESULTS

Pilot study for PCR screening tests for MRSA. At the request of the Infection Prevention Office, a pilot program was instituted to screen new SICU and PICU patients for nasal carriage of MRSA. The Cepheid MRSA GeneXpert® assay was employed. Briefly, for specimen collection, Copan dual swabs were used to sample each nostril as recommended for testing with the Cepheid GeneXpert® MRSA kit. Swabs were immediately transported to the laboratory and the GeneXpert® MRSA assay was employed to determine carriage. Typically, results were reported within 2 hours of admission. MRSA positive patients were then placed under appropriate precautions as described above.[9]

Cost of Screening. As shown in Table 1, the costs of standard microbiological and PCR-based testing were compared. Labor costs associated with processing and preparation of samples as well as reporting of results were estimated based on experience at the institution and are in agreement with costs reported previously.[11] During this three month period of September-November, 2011, a total of 333 patients admitted to the SICU were screened, with 35 (10.5%) positive MRSA carriers identified. A total of 156 PICU admissions were screened, with 27 (17.3%) MRSA positive patients identified. The SICU reported 2 MRSA HAIs during the pilot study period, for an average of 0.6 HA MRSA/month. During the previous 7 month period (January-August, 2011) when no screening was done, the SICU reported a rate of 3 HA MRSA/month. During the 3 month pilot study, 2 HA MRSA infections were reported in the PICU, neither of whom was screened by the PCR test protocol. Excluding these two missed tests, none of the 156 screened infants developed an HA MRSA. Of screened PICU admissions, a rate of 0 HA MRSA/month compared well to the average of 0.5 HA MRSA/month in the previous 7 month period.

Cost per MRSA carrier identified. In order to estimate the cost of identification of colonized patients, the total cost of the three month PCR screening program was divided by the total number of MRSA carriers identified (Table 2). As shown in Table 2, cost was estimated at $602.95/positive detected based on PCR costs (62 positives detected, total $37,383/489 samples tested). Using the same for number of positives and samples tested, the cost of identification by traditional microbiological screening methods was estimated as $364.30/positive detected (62 positives detected, total $22,586.70/489 samples tested).

Length of stay. The number of MRSA infections identified during the 7 months prior to initiation of the pilot program was used as a historical cohort. Patients screened via PCR or medical records were included in the pilot cohort. As shown in Table 3, there were 136 patients admitted to the hospital with a previous history of colonization with MRSA. These patients were identified and infection control practices were implemented to prevent active infection. A total of 34 patients were identified with MRSA HAIs. The median length of stay (LOS) for patients previously identified as colonized with MRSA was 6.0 days (8.86 mean LOS), compared to 29.5 days (34.85 mean LOS) for patients with either undetected colonization or MRSA HAIs. In addition, 94 patients were identified who developed HAIs with MSSA. Their median LOS was 6.5 days (16.26 mean length of stay).

Table 1. Cost of screening PICU and SICU patients for MRSA.

Category	Itemized list of expenses	Chromogenic Agar	Cepheid GeneXpert® MRSA Assay
Laboratory supplies	Swab	$1.00	$1.00
	Chromogenic agar	$2.00	
	Assay cassette		$36.00
Laboratory Technologist Time	Average hourly (wage+fringe+overhead)	$29.60	$29.60
	Labor time (accession to NEG. report)	15 min	15 min
	Labor time (accession to POS. report)	30 min	15 min
	Laboratory staff total cost/test	$7.40/neg $14.80/pos.	$7.40
Nurse collection time	Average RN hourly wage + fringe	$30.00	$30.00
	Labor time per swab	5 min	5 min
	Nurse staff total cost/test	$2.50	$2.50
Total cost/test	Laboratory supplies+tech time+nurse time	$12.90/neg $30.30/pos	$47.00/neg. or pos
	Number of PICU admissions	156/3 mo	156/3 mo
	Number of SICU admissions	333/3 mo	333/3 mo
	Total number of tests	489	489
Total cost of tests		$8186.70	$22,983.00
	Screened	$6308.10	Same for
	Positive	$1878.60 (62pos.)	Screened and Pos
Overhead	Average annual cost of Cepheid GeneXpert® on warranty	N/A	$3000/mo.
Management	1 FTE infection control nurse	$30.00/hr, 3 mo.	$30.00/hr,3 mo.
TOTAL COSTS OF SCREENING		$22,586.70	$37,383.00

Abbreviations: PICU, pediatric intensive care unit; SICU, surgical intensive care unit; neg, negative; pos, positive; mo, months.

DISCUSSION

There are a number of ways in which the economic impact of MRSA testing can be examined. The cost-effectiveness analysis method is used to determine which health interventions provide the most effective care given the cost. The analysis includes a detailed examination of the actual costs of the intervention. In the case of treatment, it is possible to estimate both the cost of prevention and the costs to treat associated with failure to intervene. These costs are frequently fixed and can be determined based on objective data. The other method of analysis is a cost-benefit analysis, which tends to be more subjective, requiring assumptions about reductions in morbidity and mortality. Such costs are generally obtained by estimation based on a number of factors such as increased hospitalization time and cost of care. Patient demographics may factor into such analysis. For example, the age and underlying condition of the patient as well as the site and type of MRSA infection may significantly influence increased costs associated with MRSA infection. However, these influences are not easily accounted for in a cost-benefit analysis.

Constant improvements to health technologies and the subsequent increase in health care costs have led to an

Table 2. Patients screened by PCR assay in a three month pilot study.

Patients Screened	Positive by PCR assay	Percent
PICU 156	27	17.3
SICU 333	35	10.5

Table 3. Comparison of Length of Stay for Patients with MRSA or MSSA Infections.

Diagnosis[1]	Number of Patients	Median Length of Stay (Range)
MRSA		
Screened on admission[2]	136	6.0 (1-92 days)
Not screened[3]	34	29.5 (6-156 days)
MSSA[3]	94	6.5 (1-216 days)

[1] Based on diagnostic code present on discharge.
[2] Identified in medical records or by PCR screening as colonized with MRSA from previous health care setting.
[3] Patients were not screened prior to or on admission, infection identified ≥ 72 hours after admission.

increasing need for cost-effectiveness analysis. This type of analysis has typically been applied to pharmaceutical costs and only recently has its usefulness in other areas of health care been appreciated.[12] Several studies have examined the cost of MRSA HAI, using a variety of parameters such as direct cost of infection[13] as well as cost of infection control.[14,15] This study evaluates the cost-effectiveness of PCR testing compared to standard culture methods for identification of MRSA colonization. In addition, the related costs associated with treatment and length of stay over a seven month period at the 722 bed hospital was examined.

There are two major points of view regarding control of MRSA by active surveillance screening: the Society for Healthcare Epidemiology of America (SHEA) supports active surveillance while the Health Care Infection Control Practices Advisor Committee recommends individual institution evaluation of surveillance.[16] Currently the second option has the most support on a state by state basis in the U.S. while the SHEA approach has been implemented in 2 states as well as the Department of Veterans Affairs.[3,4,17,18,19]

Two studies have directly examined cost-effectiveness analysis of the role of rapid testing by PCR based methods on hospital acquired MRSA infections. The first study by Brown and Paladino[20] used meta-analysis of the literature to compare the effect of the Cepheid GeneXpert® MRSA/SA blood culture PCR assay to the cost of traditional empiric therapy. They report that PCR testing for MRSA may reduce mortality rates while reducing costs compared to empiric vancomycin therapy in both the U.S. and the European Union. Further, this study included a wide range of MRSA prevalence rates and associated mortality as well as PCR costs. The second study by Kang and colleagues[11] examined the targeted approach recommended by the Health Care Infection Control Practices Advisor Committee to determine the cost-effectiveness using a decision model. In their studies, a one way sensitivity analysis found that targeted surveillance screening was associated with lower costs and resulted in better outcomes for preventing MRSA HAI. They also report that universal screening was associated with an incremental cost-effectiveness ratio of $14,955 per MRSA HAI.

A methodology similar to that of Kang and colleagues[11] was employed to determine cost-effectiveness of universal surveillance by the Cepheid Gene Xpert® MRSA PCR assay. At the institution, the cost of targeted screening of ICU and surgical admissions for a 3 month period by CHROMagar methods was less expensive than PCR testing, $22,586.70 vs $37,383.00. Initial costs to the clinical laboratory were evaluated based on the tests performed and the associated staff time. As shown in Table 1, the cost of PCR testing using the Cepheid GeneXpert® MRSA screening test is significantly more expensive than microbiological culture. However, several factors should be considered in any decision to employ this technology. Turn-around time for traditional microbiological techniques is usually 24-48 hours, compared to 2-4 hours for PCR assays. PCR testing has the advantage of rapidity, enabling the intervention of infection control staff. This parameter is not easily quantified and has two components: prevention of infection and reduced time to appropriate treatment.

Identification of previously colonized patients at the institution based on medical records equates to a turn-around time of essentially zero and patients were placed on special precautions. It is not possible to determine the extent to which MRSA diagnosis contributed to LOS based on discharge codes. These codes which were present on admission do not necessarily reflect active

infection but rather colonization requiring infection control protocols. As discussed above and shown in Table 3, patients identified as colonized with MRSA and patients who developed MSSA infections had 6 and 6.5 day median LOS compared to 29.5 day median LOS for patients who developed MRSA HAIs. Based on data available from the institution, an average cost for a given LOS, not stratified by diagnosis, was estimated for January, 2011-June, 2012. Since we were unable to assign specific cost increases associated with MRSA/MSSA infection, the large number of encounters (patients with known LOS) allowed us to estimate patient hospitalization costs for a period spanning the time frame of the current study. The average total cost for LOS of patients at the institution for 6 days (calculated from 2,260 encounters) was $14,561, for 29-30 days (110 encounters) was $63,810, and for 6-7 days (3,897 encounters) was $15,395. The LOS is significantly different for patients with previously identified MRSA or MSSA HAIs versus patients with MRSA HAIs and the costs associated with these differences can be inferred. However, a direct argument for PCR testing cannot be made. PCR screening on admission in our pilot study of intensive care units, however, did reveal a significant decrease in the number of MRSA HAIs.

The total cost of implementing PCR testing can be offset by the addition of other assays and protocols. For this analysis, we used only the MRSA testing capability of the Cepheid PCR system. However, there are a number of additional routine tests that can be performed with this instrument, including tests for influenza, *Clostridum difficile* (both epidemic strain identification and toxin genes), vanA resistance, MRSA/SA (skin and soft tissue as well as blood culture), enteroviral meningitis, group B streptococci, and Factors II and V for thrombosis. When considering the cost of testing, the cost per test would be greatly reduced if the cost of the instrument and its associated service contract were shared by other testing. In addition, costs may not be extrapolated to all health care providers based on potential differences in bulk purchase of reagents.

MRSA infections are one of the six categories of HAIs identified by the Department of Health and Human Services as targets for prevention at a national level.[21] The majority of MRSA (~60%) nosocomial infections occur among patients in the intensive care units.[22] Our pilot screening program was deployed for patients being admitted to critical care, i.e., the surgical and pediatric intensive care units. Results show a marked decrease in HAIs in both these populations, although not statistically significant due to the low sampling size.

At the institution, most MRSA-infected patients were treated with vancomycin for a standard course of therapy. As noted by Brown and Paladino,[20] universal screening is superior to empiric vancomycin therapy as a strategy for reducing costs associated with MRSA HAIs. It has been previously shown that the cost of vancomycin therapy for MRSA versus MSSA infections differ substantially.[23] The treatment of choice for MRSA infections is vancomycin, although there may be a number of mitigating factors in its use. At the institution, vancomycin-resistant MRSA is infrequently observed. Thus, this relatively low cost drug is the first line therapy for MRSA infections. Indeed, the Infectious Diseases Society of America (IDSA) guidelines recommend vancomycin (or daptomycin) for the treatment of MRSA bacteremia or other invasive infections.[11] For patients who do not tolerate vancomycin or those with potentially heteroresistant strains, several other agents offer acceptable alternatives (Table 4). However, the cost of these alternative therapeutic approaches may be much higher.

Table 4. Antibiotic costs associated with treatment of MRSA.

Drug	Dose	Cost/Dose ($USD)	Duration (days)	Total Cost ($USD)
Vancomycin	1 gram q12h	$3.30	14	$92.40
Daptomycin*	500 mg q24h	$285.00	14	$6840.00
Linezolid (Oral)	600 mg q12h	$94.50	14	$2646.00
Linezolid (IV)	600 mg q12h	$108.66	14	$3042.00
Tigecycline	50 mg q12h	$76.58	14	$2144.00

*6 mg/kg

Different types of infection may be more or less expensive than the estimates here. For example, MRSA infections may include bacteremia, skin and soft tissue infections (SSTI), ventilator associated pneumonia (VAP), catheter-related infections, osteomyelitis, endocarditis, or meningitis. Each of these specific diagnoses would require potentially different treatment regimens predicated on such parameters as length of treatment, choice of drug, patient co-morbidities, and clinical response. Monitoring of vancomycin trough concentrations is also recommended. Trough

concentrations are typically drawn before the third or fourth dose, a time where steady-state concentrations have generally been achieved. Once a therapeutic concentration has been achieved, serum concentrations are generally measured weekly or if patient status changes. Similarly, monitoring for nephrotoxicity is performed, adding to the overall cost of empiric treatment.

Excessive health care costs in the form of patient morbidity and mortality have been attributed to HAIs. Models that try to estimate the independent effect of HAI on length of hospital stay and cost are difficult due to inherent bias.[24] For example, patients with an HAI may have comorbid conditions that substantially influence both LOS and total cost. The results report LOS without the extensive medical chart review necessary to attribute specific costs to specific diagnosis. Indeed, it is debatable if such distinctions could be made and comparative attribution studies have been preferred.[15,25] However, in this study patients with MRSA colonization/infection identified on admission had shorter LOS compared to a matched group of MRSA infected patients who were not identified or screened and did not receive prophylactic measures to prevent MRSA infection.

It should be noted that there are several limitations in this study. A relatively short time period was employed for the pilot study of PCR testing for MRSA colonization. The patient population was limited to high risk groups admitted to the SICU and PICU. Screening of a general admission population by PCR would increase the number of tests performed and the cost effectiveness would be subsequently influenced by the percent prevalence of MRSA colonization in the population.[20] The decrease in turn-around time for identification of MRSA carriers is considerably shorter than that for traditional microbiological testing. However, quantitation of this parameter is difficult to determine. At the institution, PCR testing was done within 1-2 hours of admission. Expanded screening of all general admissions could require batching of tests, increasing the actual turn-around time.

The extent to which protocols are accepted and employed by the institution may also influence cost effectiveness. For example, in this study, results from the PICU were complicated by a failure to screen all admissions, contrary to protocol, which resulted in two MRSA HAIs. Since this study did not employ an extensive chart review of all patient records in an effort to attribute specific hospital costs to MRSA/MSSA infection, hospital costs associated with LOS cannot be directly correlated with MRSA screening. However, analysis based on differences in LOS suggests an associated savings in hospitalization costs: MRSA HAI with 29.5 day LOS at $63,810 versus MRSA identified on admission with 6 day LOS at $14,561, a difference of $49,249 per hospitalization. Although our pilot study was small and it is not possible to directly relate the cost-effectiveness and cost-benefit analyses due to confounding factors, a reduction of 2.9 MRSA/month associated with PCR screening suggests potential savings in hospitalization costs of $142,822 per month.

While this is a relatively specific analysis for an academic institution, actual costs of testing and a prototype for evaluation in other hospital settings can be examined in a similar fashion. Although each setting is unique, this study may provide a guide for laboratory directors and administrators involved in critical cost-effectiveness studies associated with selection of new technologies and standards.

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