Risk Factors for Clinical Infection in Patients colonized with Methicillin Resistant Staphylococcus aureus (MRSA)

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Abstract

Objective: To identify the risk factors involved in development of infection in individuals colonized with Methicillin-resistant Staphylococcus aureus (MRSA) among intensive care unit (ICU) patients.

Methods: A total of 1431 patients were admitted in ICU of which 63 grew MRSA during January 1998 to December 1999. Patients who developed infection with MRSA in less than 48 hours of their admission to ICU were excluded. Medical records of all patients who grew MRSA were reviewed and 57 patients were identified for inclusion in the study. Thirty-seven of these had features of infection with MRSA and were selected as cases and 20 were identified as asymptomatic colonizers and labeled as controls. Risk factors like age of the patient, duration of ICU stay, gender, co-morbidity, presence and duration of central lines, number of arterial-punctures and number and duration of intubations were compared between cases and controls.

Results: Cases were found to be significantly older (52.8±15.1) than controls (34.9±21.2). Other identified risk factors were diabetes mellitus (p=0.001) and the first 15 days of central line placement (p=0.025). Although chronic liver disease and hypertension could not be identified as significant risk factors, they clearly showed association. Other risk factors were not significantly different from controls.

Conclusion: It is suggested that greater care is required for the elderly, diabetic patients with a central venous line in place especially during the first fifteen days of its introduction (JPMA 54:408;2004).

Introduction

Staphylococcus aureus was first described as a bacterial agent of infection in 1882.[1] Currently, S. aureus is one of the most common causes of community-acquired and nosocomial infections in the world.[2,3] Penicillin resistant S. aureus emerged soon after the introduction of penicillin into clinical practice.[4] In 1960, the first strains resistant to methicillin were isolated in London.[5] The incidence of methicillin resistant strain of Staphylococcus aureus (MRSA) infections is increasing ever since.[6] The resistance of S. aureus has become most alarming for the medical community, especially since vancomycin resistance is also emerging.[2,7,8] The first case of vancomycin-intermediate S. aureus (VISA) was reported in 1996 from Japan.[9] In North America, the proportion of MRSA infections rose from 2.4% in 1975 to 29% in 1991.[10] The percentage of MRSA in US intensive care units (ICUs) has increased from 30% to 40% in the mid-1990s to 46.7% in 1998.[11] MRSA has been implicated relatively frequently in hospital outbreaks.[10] A study done by a laboratory-based surveillance program showed significantly higher prevalence of MRSA in ICUs patients (35.2%) than in non-ICU inpatients (31.9%; P<0.01).[12] The European Prevalence of Infection in Intensive Care (EPIC) study showed an average rate of 59.6% in ICUs and the highest prevalence (81%) was found in Italy.[13] In hospital outbreaks of MRSA, many patients are initially colonized without infection.[7] Though the risk factors for MRSA colonization are well described by many studies, the reasons why some progress to infection and others do not, still remain unclear.[14,15] Intensive measures for controlling the risk factors involved in the progression of colonization to infection are perhaps the only realistic method of effectively minimizing the associated morbidity and mortality. Controlling these risk factors has already shown effective useful, feasible and cost-effective results.[16] To the best of our knowledge, published data on MRSA in critical care units in Pakistan is non-existent. However, a multi-centre study on the community prevalence of MRSA has reported it to be as high as 61%, particularly in large urban centres, along with a virtual absence of any vancomycin resistance among strains from across the country.[17] The present study was done to identify some of the risk factors involved in development of overt infection in contrast to benign colonization in exposed ICU patients with MRSA.

Material and Methods

This is a retrospective case-control study carried out at The Aga Khan University Hospital (AKUH). The study population included patients admitted to the intensive care unit (ICU) of AKUH during the two-year period from January 1998 to December 1999. The files of all the patients who were found MRSA positive at any time during their ICU stay at AKUH were reviewed with the help of a structured questionnaire. The patients were divided into cases and controls. Cases were identified by the presence of clinically significant infection with MRSA at any time during their ICU stay. Infection was defined as the isolation, on culture, of MRSA from any part of the body in the presence

on culture, of MRSA from any part of the body in the presence of signs and symptoms of the associated disease or from sterile sites [cerebrospinal fluid (CSF) and blood] even in absence of signs and symptoms. The latter group was included to ensure that patients with real infection, whose symptoms were masked by concurrent administration of various drugs (e.g. steroids, cytotoxics or broad spectrum antibiotics), were not missed. In either case, it was mandatory that the culture was repeated at least once and that the signs and symptoms, if present, could not be explained by the simultaneous isolation of another organism. The diagnosis of MRSA infection was determined by reviewing doctor's notes and orders and microbiological reports and considering the patient's symptoms.

The patients were labeled as controls when they remained colonized with MRSA but did not develop infection at any time during their ICU stay. Colonization was defined as the isolation of MRSA, documented by its growth in culture (culture positivity), from non-sterile sites in the absence of signs and symptoms of the associated disease. The colonization status was determined from doctor's notes and orders, tracheal aspirates, and microbiological reports of other sites of colonization like wounds and nasal swabs. The patients who had clinically significant infection with MRSA in less than 48 hours of their hospital admission were excluded from the study to allow a controlled study of the risk factors operative in the ICU setting.

Data was analyzed using the SPSS statistical software package, version 10.0 for Windows (SPSS. Inc, Chicago, IL). The risk factors like age, gender, co-morbidity e.g. diabetes mellitus (DM), ischemic heart disease (IHD), hypertension (HTN), chronic renal failure (CRF), chronic liver disease (CLD), presence of prostheses, use of steroids, and broad spectrum antibiotics, dialysis, duration of ICU stay, presence and duration of central lines, total number and duration of intubations and number of arterial punctures were compared amongst the cases and controls. Age of cases and controls was compared using non-parametric tests (Wilcoxon statistic), duration of ICU stay using ANOVA and others using chi-square test. Odds ratio (OR) with the 95% confidence interval for OR (CI) was also calculated for all the tested variables.

Results

Of the 1431 patients admitted to the ICU of AKUH from 1998 to 1999, 63 were found to be culture positive for MRSA (prevalence = 4.4%), of which 6 patients developed clinical signs and symptoms of infection within 48 hours of admission and were thus excluded. Of the rest, we identified 37 cases and 20 controls as MRSA carriers. The prevalence of different risk factors in both cases and controls are described in table 1. It was found that the cases were in general older (mean age of 52.8 years with standard deviation ($\pm$) 15.1 years) than the controls (34.9$\pm$21.2 years), $p<0.003$ (Table 2).

No significant difference was found in the gender distribution and the duration of ICU stay among the study groups. Diabetes mellitus was identified as the major risk factor for the MRSA infection with 16 (43.2%) cases and only 2 (10.0%) controls being diabetic. A history of Ischemic heart disease or hypertension was not documented in all the files reviewed; moreover, the review of the available data could not yield a significant difference between the cases and the controls. Similarly, no significant differences were observed regarding the effects of chronic renal failure and dialysis on MRSA infection. Use of steroids in ICU patients were tested as a risk factor for developing infection but no difference was found in steroid use amongst the cases and controls since 13 (35.1%) of the cases and 7 (35.0%) controls were exposed to steroids during their ICU stay. Chronic liver disease was more prevalent in cases than in controls [4 (10.8%) vs. 1 (5.0%); OR=2.3], yet this difference was not statistically significant (p=0.459). Use of broad-spectrum antibiotics prior to the full-blown infection was present in all the cases but only in 18 (90%) controls and the difference did not appear to be significant (p=0.12).

The presence of a central line was tested as an independent risk factor for the development of MRSA infection, which was present in 29 (78.4%) cases and 14 (70.0%) controls, a difference that was again not meaningful. Duration of central line was also analyzed in both groups for its impact on development of infection. The mean duration of central line till the end-point of infection or discharge from the ICU (whichever developed first) was 9.96$\pm$6.99 days for cases and 12.83$\pm$8.46 days for controls. We observed that 5 (17.2%) patients from amongst the cases and 7 (50.0%) patients in control group had more than 15 days of application of a central venous line, a difference that was significant (p=0.025).

The total number of arterial punctures before the development of infection was analyzed as a risk factor for MRSA infection. The mean number of arterial punctures for cases was 36.97$\pm$23.17 and 59.75$\pm$55.67 for the controls. It was noted that amongst all records with a complete record of arterial punctures, 9 (25.7%) of 35 cases had more than 50 arterial punctures as compared to 5 (38.5%) of 13 controls.

All of our identified cases and controls had been intubated at least once in their stay in the ICU. The mean number of intubations till the end-point of infection or discharge was 1.89$\pm$0.71 for cases and for controls was 2.0$\pm$1.34. The mean duration of intubations came out to be 21.11$\pm$17.92 days for cases and 28.35$\pm$34.64 days for con-

discharge was 1.89±0.71 for cases and for controls was 2.0±1.34. The mean duration of intubations came out to be 21.11±17.92 days for cases and 28.35±34.64 days for controls. The duration of more than thirty days was tested as a risk factor and was seen in 8 (21.6%) of the cases and 5 (25.0%) of the controls, a difference with no statistical significance.

Discussion

The risk factors considered in our study are largely independent of each other, as we have controlled for much of the confounding that was inevitable, had we not restricted our study sample to patients in the ICU only.[18] Our study suggests significant differences between the cases and controls in terms of age distribution, the presence of diabetes mellitus and the duration of a central venous line. The first two results are in contrast to those of Coello, R. et al,[18] who, in a prospective cohort study, failed to find an association between the presence in MRSA colonizers, of diabetes mellitus (DM) and the subsequent progression to MRSA infection. The relationship between DM and staphylococcal infections is, however, well documented and known for many years.[19-23] Our study therefore, seems to reiterate the importance of strict infection control and early decontamination in diabetics colonized with MRSA, so as to minimize the costs and the increased morbidity and mortality subsequent to the development of clinical infection.

As far as age is concerned, the difference of results between our study and that of Coello et al may be due to the difference between the study populations, or to the fact that the variable has been analyzed differently in the two studies (i.e. as a continuous variable in our study, using non-parametric tests vs. as a grouped variable in the Coello cohort). According to our results, the patients who eventually develop the infection are, in general, older than those who do not.

In comparing the total duration of intubation and indwelling central venous lines, the choice of end-point for the cases and controls is different. This may appear to introduce systematic bias in the results of the study by potentially increasing the average duration of intervention in controls. However, in case the controls were found to survive the extended intervention (intubation or central line) than the control, it may likely indicate a constitutive difference (e.g. immunological, genetic etc.) amongst the two groups in terms of resistance to the development of infection. Nevertheless, our study failed to show any such differences.

The infection generally tends to develop within the first fifteen days of the administration of a central venous line, with far fewer new infections developing during the subsequent period. This perhaps implies that the first fifteen days after harboring of MRSA are the most crucial as far as the progression of the carrier status to actual infection is concerned, the colonization thereafter becoming more of a symbiotic state. Thus this should be the period of greatest vigilance and prophylaxis.

We had hypothesized that the multiplicity of arterial punctures for the purposes of arterial blood-gas determination might be an independent risk factor. This study however, fails to find any significance attributable to the total number of arterial punctures. It is our opinion that further investigation with a larger sample is required to uncover this difference of effect as a clear pattern emerged in our data, with most of the cases being concentrated in the bracket of subjects with no more than 50 arterial blood gas determinations. This study also could not identify the CLD as an independent risk factor for the progression to MRSA infection, though a trend (OR=2.3) was observed. A study with larger sample size might be able to see this difference as significant.

In the end, we recommend that greater vigilance be exercised with older, diabetic patients and particularly during the first fifteen days of insertion of a central venous line. The ICU physician should have a low threshold for starting off empiric anti-MRSA therapy in such patients, should signs of infection become apparent. Early initiation of rigorous treatment is likely to markedly reduce the ensuing morbidity and mortality.

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