PATIENT-ASSOCIATED RISK FACTORS FOR ACQUISITION OF METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) IN A TERTIARY HOSPITAL SETTING

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MRSA is a dominant hospital pathogen because of its increasing incidence, the cost of treatment, antibiotic resistance, limited antimicrobial armamentarium, and associated increased mortality. Determining risk factors for MRSA acquisition in hospital settings has important public health relevance for defining targets for infection control, reduction in mortality from hospital-acquired infections, and decreasing hospitalization costs. A retrospective matched case-control study was initiated to determine patient-associated risk factors for MRSA acquisition at the Presbyterian University Hospital. It was hypothesized that risk factors for MRSA acquisition could be identified and used to enhance or tailor infection control strategies. Cases and two matched controls were selected among patients admitted to high risk units where MRSA screening was routinely done from January 2001 to December 2008. Cases were subjects who acquired MRSA during hospitalization. Variables collected were potential patient-associated risk factors associated with MRSA acquisition among cases versus controls. The odds of exposure to potential risk factors for MRSA acquisition were compared between cases and controls, using matched univariate conditional logistic regression. A single multivariate conditional logistic regression model identifying patient-specific risk factors significantly associated with MRSA acquisition was generated.

The final model included 15 independently significant variables. Seven factors were positively associated with MRSA acquisition: primary diagnosis of respiratory disease, digestive tract disease, or injury/trauma, any diagnosis of pneumonia, cerebrovascular/peripheral vascular disease, intracranial ventricular shunt procedure, and a high risk unit stay prior to index culture. Eight variables were protective and included two beta lactam antibiotic classes (penicillin and cephalosporin), rifamycin, daptomycin/linezolid, proton pump inhibitors, history of transplant, extracorporeal membrane oxygenation, and intravascular stenting/catheterization. As 3 of the 7 factors positively associated with MRSA acquisition were conditions present on admission, they were not modifiable. Of the remaining 4, pneumonia could potentially be reduced by maintaining high compliance with pneumococcal vaccine. Admission to a high risk unit in itself is not modifiable. Although ventricular shunting was a factor, the lack of association with many common bedside or interventional procedures performed in these high risk areas argues for intensified environmental control and strict sterile technique for all procedures performed on patients.

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1.0 BACKGROUND

Methicillin resistant *Staphylococcus aureus* (MRSA) is an important pathogen that continues to cause substantial morbidity and mortality among patients and to beleaguer infection control preventionists since it emerged in the healthcare setting decades ago [1]. It causes a broad spectrum of community-associated and healthcare-associated infections, including pyogenic infections of skin and soft tissues, pneumonia, and bacteremia, and is a leading cause of hospital-acquired infections in the United States and worldwide [2-4]. MRSA is an important public health problem because of its increasing incidence, the cost of treating MRSA infections, its resistance to antibiotics, the limited antimicrobial armamentarium directed against MRSA, and associated increased mortality [5-9].

MRSA colonization increases infection risk and MRSA colonized individuals can be reservoirs for transmission in healthcare facilities [10-11]. Collective risk factors for MRSA acquisition previously identified include MRSA colonization pressure (i.e. the proportion of other patients colonized), care workload, and antibiotic pressure (defined daily dose per 1000 patient days) [12-16]. Individual patient risk factors for MRSA acquisition or colonization previously identified include length of hospital stay; the presence of open wounds or skin ulcers; admission to a trauma unit; the presence of a tracheostomy or use of nasoenteric feeding tubes; a high Omega Score (a composite score of commonly performed hospital procedures); a high Acute Physiology and Chronic Health Evaluation II (APACHE II) score or new Simplified Acute Physiology Score (SAPS II); exposure to a roommate with MRSA; dependency in feeding, continence, and ambulation; and fluoroquinolone use [15, 17-24]. Some of the studies that identified these risk factors involved only specific settings or populations, such as surgical intensive care units (ICUs) or transplant populations, and were not always applicable to our setting. Most had small numbers of patients known to recently acquire MRSA (converters). Moreover, not all of the reporting facilities actively surveyed patients for MRSA, which limits the ability to accurately assess colonization status and /or time of MRSA acquisition.

Surveillance data at the University of Pittsburgh Medical Center (UPMC) Presbyterian University Hospital from 2005 to 2008 revealed an average MRSA hospital acquisition rate of less than 2%. Although this rate is relatively low, the challenge facing hospitals today is to get rates as close to zero as possible. With this in mind, a retrospective study with a matched case-control study design was initiated

to determine patient-associated risk factors for acquisition of MRSA at our hospital despite current infection control efforts. It was hypothesized that MRSA acquisition could decrease if modifiable risk factors were identified. The study was approved by the UPMC Total Quality Council as a quality improvement project.

With more than 7 years of culture data from our MRSA active surveillance program and a rich database of electronic health records, this study would have comparatively greater power to define patient-associated risk factors for MRSA acquisition than previous studies. Determining risk factors for MRSA acquisition in hospital settings has important public health relevance for reduction in mortality from hospital-acquired infections and decreasing costs of hospitalization. Identifying these risk factors could help determine new strategies for infection control interventions in our hospital as well as other similar hospital settings. For example, if specific medical or surgical procedures or specific subpopulations could be identified, well designed tailored enhanced infection control strategies could be applied to reduce the risk of MRSA acquisition.

2.0 METHODS

2.1 SETTING AND POPULATION

The UPMC Presbyterian University Hospital (PUH), a 766-bed tertiary care teaching facility with 156 ICU beds, utilizes an MRSA prevention bundle that has been implemented in phases since 2001. Patients with a hospital stay in high risk areas and those admitted from outside high risk facilities (long-term care, other health-care facilities) undergo active surveillance testing (AST) for MRSA nasal colonization. High risk areas are those units historically identified by the UPMC Infection Control Department as having patient populations with higher MRSA hospital-acquired infection rates. Patients admitted to high risk areas are cultured on admission, weekly, and upon discharge from the high-risk area while those admitted from high risk facilities are screened on hospital admission. AST was first implemented in the medical ICU. As additional high risk areas were identified, MRSA AST was commenced over time. High risk areas at PUH now include all ICUs (medical, surgical, cardiothoracic, neurosurgical/neurology, solid organ transplant, coronary care, and trauma), the orthopedic unit, and medical step down patient care areas.

2.2 ROUTINE MICROBIOLOGY METHODS

Both anterior nares are swabbed with sterile cotton-tipped culturettes (Becton Dickinson (BD) Diagnostic Systems, Franklin Lakes, NJ). Specimens are plated on BBL CHROMagar MRSA media (BD) and incubated overnight. Culture growth of pink or mauve colonies is considered MRSA positive. Blood and body fluid cultures are incubated in the automated BD BACTEC Instrumented Blood Culture System (BD) and clinical specimens from various body sites are planted and incubated on BBL trypticase soy agar with 5% sheep blood (BD). Coagulase-positive staphylococci are tested for oxacillin resistance by plating and incubating isolates on a BBL Oxacillin Screen Agar plate (BD) and the Kirby Bauer disk diffusion method.

2.3 DEFINITIONS AND INFECTION CONTROL PRACTICES

Patients are considered to have pre-existing MRSA if they are known or found to be MRSA colonized or infected within 2 days of hospital admission. MRSA hospital acquisition is said to have occurred and a patient considered to be a converter if found to be MRSA colonized or infected 3 or more days after admission to the hospital or high risk area. Patients known or determined to be colonized or infected with MRSA are placed in droplet contact precautions, either in a private room or cohorted with other MRSA colonized or infected patients.

2.4 SELECTION OF CASES AND CONTROLS

Cases and controls were selected using de-identified datasets from the UPMC electronic health record database, using an algorithm that was programmed based on inclusion and exclusion criteria. Patients admitted to high risk units where AST was being performed and who had nasal screening cultures for MRSA or clinical cultures that were positive for MRSA from January 2001 to December 2008 were identified as potential subjects. Cases were defined as MRSA converters who fulfilled the following inclusion criteria: presence of at least one prior negative MRSA nasal surveillance culture during the hospital admission and a subsequent positive MRSA culture, whether nasal or a clinical culture from any body site, occurring 3 or more days after hospital admission. Potential cases were excluded if they had a concurrent MRSA positive culture on the same day as their negative MRSA nasal surveillance culture and if they had a prior documented MRSA history or culture. Inclusion criteria for controls were the presence of at least one negative nasal surveillance culture taken 3 or more days after hospital admission. Subjects were excluded from being a control if they had a concurrent MRSA positive culture, a prior documented MRSA history or culture, or a subsequent positive MRSA culture within the study period. Two unique controls for each case were chosen when possible, individually matched to the case by (1) the date the index negative culture was received at the laboratory, which had to be within 7 days of the case's index positive culture, (2) patient location in the same or the closest similar hospital unit at the time of culture (i.e., a medical ICU (MICU) patient was matched to a control in an adjacent MICU and would not be matched with a patient in a surgical ICU), and (3) a minimum duration of stay, i.e. the control should have stayed in the hospital at least the same number of days between the case's last negative culture and index MRSA culture (Figure 1). Index culture refers to the first positive culture for the cases and the corresponding negative culture for the controls, and culture dates were considered the date the culture

specimen was received at the microbiology laboratory. For the cases, prior negative cultures could be taken at any time and in any unit location during the hospitalization, and for both cases and controls, the index culture could be received at any time during the admission to the high-risk unit, as long as it was 3 or more days from the hospital admit date. The hospitalization during which the cases and controls were identified was considered the index admission. Cases for which a matching control could not be identified were excluded from the analyses.

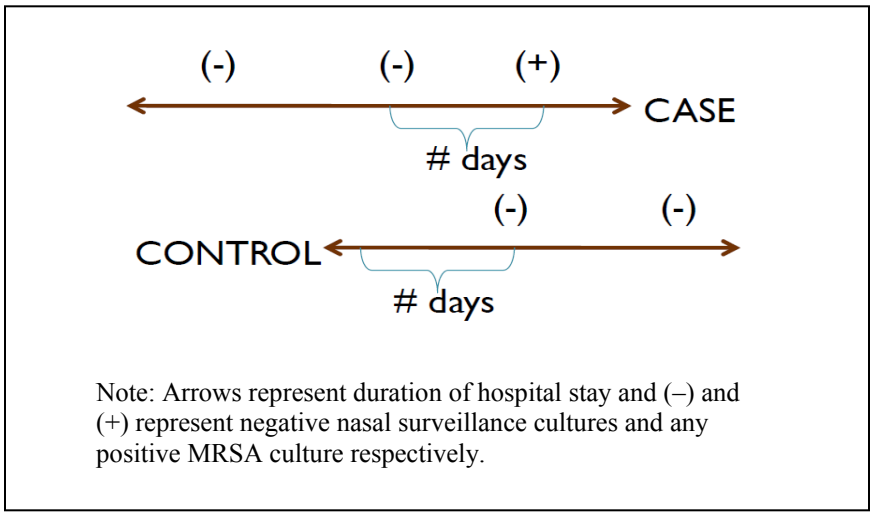

Figure 1. Method for Matching Cases and Controls Utilizing a Minimum Duration of Stay

2.5 SUBSET ANALYSIS

A subset of cases whose negative nasal surveillance cultures and subsequent MRSA positive cultures were obtained during a contiguous high risk unit stay and whose positive cultures were obtained 3 or more days after admission to a high risk unit was analyzed, along with their matched controls. Another subset of cases that were defined as converters based on a subsequent positive MRSA nasal surveillance culture, excluding those cases identified by subsequent MRSA positive clinical cultures from other body sites, was also analyzed, along with their matched controls. These subset analyses were performed to confirm the results of the larger dataset and to reduce the chance of detection bias in determining conversion from a negative to a positive MRSA status.

2.6 DEFINITIONS AND COLLECTION OF DATA

Variables collected were potential patient-associated risk factors associated with the acquisition of MRSA. All data were obtained from the UPMC electronic health record database, guided by a data collection tool. No subject interviews were conducted. Datasets were de-identified by an honest broker and data collectors were blinded to the case/control status of the subjects. Demographic data collected included age, sex, and race. Information regarding hospitalization were collected, and included admission from a long-term care facility, status of admission (elective, urgent, or emergent), admitting service (medical, surgical or other), unit locations (defined as high risk or non-high risk by the Infection Control Department), the primary diagnosis which kept the patient in the hospital, duration of entire hospital stay, duration of hospital stay until the date of the index culture, other UPMC hospitalizations in the past 6 months, and whether alive or deceased at discharge. For subjects who had a length of stay in either a high risk or non-high risk unit prior to the index culture, cumulative duration of stay in a high or non-high risk unit was calculated until the date of the index culture.

Comorbid illnesses and conditions present on admission were noted, based on combined data from ICD9 diagnostic and procedure codes documented during index and prior admissions, ICD9 main diagnostic categories, and hospital charges [25-27]. Diabetes mellitus, chronic kidney disease, cirrhosis, malignancy, chronic obstructive pulmonary disease (COPD), HIV/AIDS, and congestive heart failure (CHF) diagnoses in the current or any prior admission were considered. A diagnosis of *C. difficile* associated disease and any substance abuse or dependence or the presence of devices such as a tracheostomy, ventricular shunt, gastrointestinal stoma, subcutaneously implanted intravenous port, intracardiac defibrillator, or pacemaker were considered in any admission within the past 6 months. Other diagnoses such as myocardial infarction, pneumonia, sepsis, infection, acute renal failure, skin ulcer (venous stasis or decubitus), and cerebrovascular or peripheral vascular disease were considered only if they were noted during the index admission. A history of transplant was classified under the variable immunosuppression if the subject had a solid organ transplant during the current or any prior admission or if bone marrow transplant was performed during an admission within 1 year of the index culture. Significant steroid use was defined as documented use of systemic steroids more than or equivalent to 40 mg of prednisone for 1 week in the past 6 months. Other causes for immunosuppression included severe primary immunodeficiencies and radiotherapy or receipt of chemotherapeutic agents or other immunosuppressive drugs within the past 6 months. The Charlson Comorbidity Index of each subject was calculated based on ICD9 codes during the index admission and adjusted for each decade of age above 50 [28].

Information was obtained from Infection Control Department records on institution of contact isolation for other multi-drug resistant organisms (MDROs) such as vancomycin resistant enterococci (VRE), *Clostridium difficile*, and multi-drug resistant *Acinetobacter baumanii* during the subject's index admission, prior to the index culture. Culture data on the isolation of other MDROs in the past 6 months prior to the index culture was also obtained from the electronic health record. Complete data for generating an established acute physiologic score were not available so laboratory values typically used for severity scores were obtained from the electronic health record to provide a partial picture of severity of illness. The laboratory values that were most abnormal within 7 days of the index culture were used and sorted into simplified categories based on cut-off values correlated with poor prognosis or higher mortality used in APACHE II and SAPS III scoring systems and prior studies, when applicable [29-31]. ICD9 codes and hospital charges were also utilized to determine procedures that were performed in the 30 days prior to the index culture, such as mechanical ventilation, Foley catheterization, dialysis, and surgeries. Surgery was considered major based on a classification system used by the Centers for Medicare & Medicaid Services (CMS) [32]. Charge codes were utilized to determine oral and intravenous antibiotic or antifungal, and topical mupirocin use in the past 6 months, H_2 blocker and proton pump inhibitor (PPI) use in the past 30 days, and vasopressor use in the past 7 days, prior to the index culture.

2.7 STATISTICAL METHODS

The frequency of dichotomous variables among the cases and controls were described as number and percentage of the total number while continuous variables were described using mean and standard deviation. The odds of exposure to potential risk factors for acquisition of MRSA were compared between the cases and controls, using univariate conditional logistic regression for both binary and continuous data, conditioning on the matched sets of subjects. Matched odds ratios (mOR) for categorical variables reflect the odds of exposure to a variable for the cases versus the controls while OR for continuous variables reflect the increase in the OR for every unit increase in the variable. Race, admitting service, primary diagnosis, and discharge disposition were analyzed as categorical variables; the p values indicate the significance of the difference of the distribution of all categories between cases and controls while mORs reflect the odds of one exposure category compared to a designated reference category. A single multivariate conditional logistic regression model to identify patient-specific risk factors that are significantly associated with MRSA acquisition was generated, using forward and backward stepwise

regression methods on variables that had a p value of < 0.10 on univariate analysis. A cut-off p value of < 0.05 was used for the final model. Selected biologically plausible interactions between covariates that were found significant on multivariate analysis were tested individually and interaction terms were added to the combined multivariate main effect logistic regression model if significant. The same statistical methods were applied in analyzing the subsets. Sample size calculations using the Pearson chi-square test for 2 proportions indicated that 235 cases and 470 controls were needed to achieve 90% power to detect an OR of 2.0 with 2-sided α of .05 . All analyses were performed using SAS 9.2 software.

3.0 RESULTS

3.1 UNIVARIATE ANALYSIS

A total of 475 cases were identified. Of these, 19 cases could not be matched to controls and were excluded from analyses. Four hundred fifty six cases and 880 matched controls comprised the main set of subjects analyzed. Some cases had only 1 control since a second eligible control based on matching criteria could not be identified. A subset of 287 cases whose index culture was a nasal surveillance culture with 553 matched controls and a second subset of 362 cases whose initial negative and subsequent positive index cultures were obtained during their high risk unit stay with 607 matched controls were also analyzed.

Overall, 27 variables were found to be significant in the univariate analysis. Table 1 shows the demographic and admission characteristics of the main set of cases and controls. On univariate analysis, admission from a long-term facility and stay in a high risk unit prior to index culture was significantly associated with MRSA acquisition whereas stay in a non-high risk unit prior to index culture was protective as was prior acquisition of VRE. Cases and controls did not differ significantly in age, sex, race, urgency of admission, admitting service, recent hospitalization at UPMC, substance abuse or dependence, age-adjusted Charlson Comorbidity Index, total abnormal or extreme laboratory values, isolation of other MDROs, contact isolation for another MDRO during hospitalization, or discharge disposition.

Table 1. Univariate Analysis of Demographic and Admission Characteristics

Variable	Odds Ratio (95% CIs)	No. (%) of Cases (n=456) or Mean ± SD	No. (%) of Controls (n=880) or Mean ± SD	p value
Age	1.00 (1.00, 1.01)	60.2 ± 17.5	59.1 ± 16.5	.27
Male Sex	0.95 (0.75, 1.20)	252 (55.3)	492 (55.9)	.68
Race	-	-	-	.99
White	1.00	335 (73.5)	649 (73.8)	-
Black	1.03 (0.70, 1.53)	42 (9.2)	79 (9.0)	-
Other or Unknown	1.00 (0.73, 1.37)	79 (17.3)	152 (17.3)	-
Emergent or Urgent Admission	1.08 (0.74, 1.57)	406 (89.0)	779 (88.5)	.68
Admission from Long-Term Care Facility	1.59 (1.04, 2.44)	42 (9.2)	51 (5.8)	.03
Admitting Service	-	-	-	.45
Medical	1.00	266 (60.2)	530 (58.3)	-
Surgical	1.15 (0.87, 1.53)	183 (40.1)	332 (37.7)	-
Other	0.71 (0.28, 1.82)	7 (1.5)	18 (2.0)	-
Length of stay (LOS) (Days)	1.00 (1.00, 1.00)	42.0 ± 53.7	44.1 ± 40.1	.43
LOS Prior to Index Culture (Days)	1.00 (1.00, 1.00)	20.9 ± 45.9	20.8 ± 25.8	.99
High Risk Unit Stay Prior to Index Culture	6.4 (2.28, 17.95)	452 (99.1)	834 (94.8)	.0004
LOS in High Risk Unit (Days)	1.00 (1.00, 1.00)	16.8 ± 44.5	15.8 ± 20.0	.67
Non-High Risk Unit Stay Prior to Index Culture	0.64 (0.50, 0.81)	198 (43.4)	475 (54.0)	.0002
LOS in Non-High Risk Unit (Days)	0.99 (0.97, 1.00)	9.6 ± 11.8	10.7 ± 15.2	.14
Other UPMC Hospitalization in Past 6 Months	0.87 (0.64, 1.19)	68 (14.9)	144 (16.4)	.39
Substance Abuse or Dependence				
Alcohol	0.84 (0.57, 1.23)	42 (9.2)	95 (10.8)	.37
Drug	1.13 (0.67, 1.93)	23 (5.0)	41 (4.7)	.65
Tobacco	0.89 (0.58, 1.37)	35 (7.7)	73 (8.3)	.59
Primary Diagnosis	-	-	-	.06
Circulatory Disease	1.00	89 (19.6)	214 (24.3)	-
Respiratory Disease	1.71 (1.16, 2.53)	103 (22.6)	152 (17.3)	-
Digestive Tract Disease	1.39 (0.89, 2.20)	49 (10.8)	87 (9.9)	-
Injury or Trauma	1.40 (0.95, 2.07)	101 (22.2)	182 (20.7)	-
Other Diagnosis[a]	1.16 (0.80, 1.67)	113 (24.8)	245 (27.8)	-

[a]Includes diseases classified under hematologv/oncology, infectious diseases, obstetrics/gynecology, rheumatology, dermatology, endocrinology, neurology, genitourinary, and psychiatry

Table 1 continued.

Variable	Odds Ratio (95% CIs)	No. (%) of Cases (n=456) or Mean ± SD	No. (%) of Controls (n=880) or Mean ± SD	p value
Age-Adjusted Charlson Comorbidity Index	0.97 (0.94, 1.01)	3.8 ± 2.9	4.0 ± 3.0	.20
Total Abnormal Laboratory Values	0.95 (0.88, 1.04)	4.5 ± 1.5	4.6 ± 1.5	.26
Albumin < 3.5 g/dL	0.90 (0.71, 1.15)	275 (60.3)	549 (62.4)	.41
Bilirubin ≥ 2 mg/dL	0.79 (0.57, 1.09)	77 (16.9)	173 (19.7)	.14
CD4 < 200 cells/mm^3	0.39 (0.10, 1.44)	5 (2.7)	16 (4.7)	.16
Creatinine < 0.6 or ≥ 1.4 mg/dL	0.89 (0.68, 1.16)	335 (73.5)	664 (75.4)	.40
Bicarbonate <22 or ≥ 32 meq/L	1.19 (0.94, 1.51)	265 (58.1)	475 (54.0)	.15
Hematocrit < 30 or ≥ 46 %	0.75 (0.44, 1.29)	430 (94.3)	841 (95.6)	.30
Potassium <3.5 or ≥ 5.5 meq/L	0.91 (0.70, 1.19)	332 (72.8)	656 (74.6)	.51
Sodium < 130 or ≥ 150 mmol/L	0.84 (0.66, 1.08)	135 (29.6)	286 (32.5)	.19
WBC < 3 or ≥ 15 X 10^9/L	0.90 (0.71, 1.14)	284 (62.3)	569 (64.7)	.38
Other MDROs Isolated in the Past 6 Months				
Vancomycin Resistant *Enterococcus*	0.75 (0.58, 0.97)	132 (29.0)	299 (34.0)	.03
C. difficile	0.88 (0.56, 1.38)	32 (7.0)	67 (7.6)	.57
Multi-drug Resistant *A. baumanii*	0.35 (0.09, 1.32)	3 (0.7)	14 (1.59)	.12
Prior Contact Isolation for Other MDROs	0.86 (0.67, 1.11)	155 (34.0)	322 (36.6)	.25
Discharge Disposition	-	-	-	.13
Alive	1.00	290 (63.6)	548 (62.3)	-
Deceased	1.10 (0.83, 1.46)	113 (24.8)	196 (22.3)	-
Unknown	0.73 (0.51, 1.04)	53 (11.6)	136 (15.4)	-

Comorbid illnesses and conditions present on admission for both groups, along with medical procedures performed in the past 30 days are presented in Table 2. Univariate analysis identified 15 significant risk factors. Four were associated with MRSA acquisition and included pneumonia, mechanical ventilation, intracranial ventricular shunt, and tube feeding. Eleven variables were identified as protective; three of these were comorbidities present on admission and included chronic kidney disease, immunosuppression, and solid organ transplant at any time (or at 12 or 6 months, data not shown) or bone marrow transplant within the past 12 months. The remaining 8 protective variables were procedures performed in the past 30 days and included peritoneal dialysis or hemodialysis, extracorporeal membrane oxygenation (ECMO), intraaortic balloon pump (IABP) or ventricular assist device placement, intravascular stenting or cardiac catheterization, trans-esophageal echocardiography (TEE), gastrointestinal endoscopy, gastrointestinal surgery, and a higher total number of major surgeries. Notably, the presence of diabetes mellitus, *C. difficile* associated disease (CDAD), acute renal failure, skin ulcers, a tracheostomy, or a central venous catheter were not significant risk factors.

Table 2. Univariate Analysis of Comorbid Illnesses, Conditions Present During Admission, and Procedures Performed in the Past 30 Days

Variable	Odds Ratio (95% CIs)	No. (%) of Cases (n=456) or Mean±/-SD	No. (%) of Controls (n=880) or Mean±/-SD	p value
Comorbidities and Conditions Present During Admission				
Myocardial Infarction	0.83 (0.63, 1.07)	114 (25.0)	253 (28.8)	.15
Congestive Heart Failure	0.90 (0.69, 1.18)	139 (30.5)	284 (32.3)	.44
Cerebrovascular or Peripheral Vascular Disease	1.27 (0.96, 1.69)	121 (26.5)	203 (23.0)	.09
Diabetes Mellitus	0.92 (0.72, 1.18)	163 (35.8)	331 (37.6)	.52
Chronic Obstructive Pulmonary Disease	1.10 (0.87, 1.40)	174 (38.2)	312 (35.4)	.41
Sepsis	1.00 (0.78, 1.28)	192 (42.1)	369 (41.9)	.98
Pneumonia	1.60 (1.26, 2.03)	271 (59.4)	429 (48.8)	.0001
Any Infection	1.11 (0.81, 1.54)	384 (84.2)	729 (82.8)	.51
C. difficile Associated Disease	0.83 (0.58, 1.19)	52 (11.4)	114 (13.0)	.31
Chronic Kidney Disease	0.66 (0.48, 0.90)	68 (14.9)	180 (20.4)	.01
Acute Renal Failure	0.89 (0.67, 1.19)	88 (19.3)	186 (21.1)	.44
Cirrhosis	0.79 (0.48, 1.30)	24 (5.3)	55 (6.2)	.35
Venous Stasis or Decubitus Ulcer	1.34 (0.98, 1.85)	75 (16.4)	113 (12.8)	.07
Immunosuppression	0.75 (0.59, 0.96)	175 (38.4)	390 (44.3)	.02
HIV/AIDS	1.15 (0.42, 3.17)	6 (1.3)	10 (1.1)	.79
History of Transplant	0.44 (0.29, 0.69)	39 (8.6)	129 (14.7)	.0003
Significant Steroid Use	0.81 (0.62, 1.04)	141 (30.9)	309 (35.1)	.10
Malignancy	0.81 (0.61, 1.07)	87 (19.1)	197 (22.4)	.14
Other[a]	0.83 (0.46, 1.49)	18 (3.8)	40 (4.6)	.53
Intracardiac Pacemaker or Defibrillator	1.12 (0.74, 1.69)	39 (8.6)	68 (7.7)	.60
Tracheostomy	1.22 (0.96, 1.56)	188 (41.2)	327 (37.2)	.11
Gastrointestinal Stoma	0.83 (0.63, 1.11)	102 (22.4)	221 (25.1)	.21
Subcutaneous Intravenous Port	0.89 (0.45, 1.76)	207 (45.4)	401 (45.6)	.73

[a]Includes immunosuppression from chemotherapy, radiotherapy, other immunosuppressive drugs, and other immunodeficiency syndromes

Table 2 continued.

Variable	Odds Ratio (95% CIs)	No. (%) of Cases (n=456) or Mean±/-SD	No. (%) of Controls (n=880) or Mean±/-SD	p value
Procedures Performed in the Past 30 Days				
Mechanical Ventilation	1.89 (1.17, 3.05)	420 (92.1)	778 (88.4)	.01
BIPAP or CPAP Noninvasive Ventilation[b]	1.05 (0.80, 1.38)	100 (21.9)	187 (21.2)	.72
Bronchoscopy	1.08 (0.85, 1.37)	234 (51.3)	438 (49.8)	.53
Chest Tube Insertion	1.02 (0.72, 1.44)	68 (14.9)	132 (15.0)	.93
Thoracentesis	0.79 (0.53, 1.17)	40 (8.8)	95 (10.8)	.24
Central Venous Catheterization	0.77 (0.56, 1.05)	368 (80.7)	743 (84.3)	.10
Peripherally Inserted Central Catheter	0.92 (0.72, 1.17)	273 (59.9)	546 (62.0)	.48
Central Venous Pressure Monitor	0.70 (0.41, 1.19)	23 (5.0)	60 (6.8)	.19
Peripheral Venous Catheterization	0.87 (0.69, 1.09)	238 (52.2)	495 (56.2)	.22
Arterial Catheterization	1.01 (0.79, 1.30)	231 (50.7)	448 (50.9)	.92
Peritoneal Dialysis or Hemodialysis	0.68 (0.50, 0.92)	82 (18.0)	211 (24.0)	.01
Foley Catheterization	1.09 (0.85, 1.41)	159 (34.9)	292 (33.2)	.50
Intracranial Ventricular Shunt Procedure	1.78 (1.05, 3.03)	33 (7.2)	42 (4.8)	.03
Laminectomy	1.10 (0.47, 2.57)	9 (2.0)	15 (1.7)	.83
Lumbar Puncture	0.76 (0.44, 1.30)	19 (4.2)	49 (5.6)	.32
Extracorporeal Membrane Oxygenation	0.42 (0.23, 0.80)	25 (5.5)	77 (8.8)	.01
IABP[b] or Ventricular Assist Device Placement	0.45 (0.26, 0.78)	20 (4.4)	75 (8.5)	.004
Intravascular Stent or Catheterization	0.68 (0.50, 0.93)	83 (18.2)	210 (23.9)	.02
Trans-Esophageal Echocardiography	0.65 (0.43, 0.99)	49 (10.7)	127 (14.4)	.04
Thrombolysis	1.02 (0.76, 1.36)	87 (19.1)	166 (18.9)	.92
Blood Transfusion	0.98 (0.75, 1.29)	347 (76.1)	673 (76.5)	.91
Gastrointestinal Endoscopy	0.62 (0.45, 0.86)	64 (14.0)	176 (20.0)	.003
Tube Feeding[c]	1.31 (1.03, 1.67)	208 (45.6)	352 (40.0)	.03
Physical, Occupational, or Respiratory Therapy	0.78 (0.57, 1.07)	369 (80.9)	739 (84.0)	.12
Major Surgery				
Cardiothoracic	0.70 (0.46, 1.07)	61 (13.4)	143 (16.2)	.10
Gastrointestinal Surgery	0.64 (0.44, 0.91)	54 (11.8)	147 (16.7)	.01
Head and Neck Surgery	1.15 (0.88, 1.51)	117 (25.7)	207 (23.5)	.31
Neurosurgery	0.83 (0.50, 1.38)	24 (5.3)	56 (6.4)	.47
Orthopedic Surgery	0.99 (0.65, 1.48)	51 (11.2)	100 (11.4)	.94
Vascular Surgery	0.90 (0.64, 1.27)	57 (12.5)	122 (13.9)	.54
Total Number of Major Surgeries	0.87 (0.76, 0.99)	0.9 ± 1.0	1.00 ± 1.0	.04

[b]Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BIPAP)
[c]Includes nasoenteric tube feeding and tube feeding through an esophageal, gastric, or small bowel stoma

Table 3 shows the univariate analysis of medication use. Seven variables were found to be significant, all protective. They included use of penicillins, cephalosporins, carbapenems, daptomycin or linezolid (anti-MRSA agents), rifamycin, antifungals, and PPI. Application of topical mupirocin, which is used for nasal decolonization of MRSA, was not significant. Analyzing antibiotic use in a shorter time period (the past 30 days as opposed to the past 6 months) resulted in a lack of significance for the anti-MRSA antibiotics daptomycin or linezolid but did not change the significantly protective OR for the beta lactam classes or rifamycin (data not shown).

Table 3. Univariate Analysis of Antibiotic and Other Medication Use

Variable	**Odds Ratio (95% CIs)**	**No. (%) of Cases (n=456)**	**No. (%) of Controls (n=880)**	**p value**
Any Intravenous or Oral Antibiotic	0.70 (0.37, 1.31)	439 (96.3)	857 (97.4)	.27
Penicillin	0.69 (0.54, 0.88)	251 (55.0)	556 (63.2)	.003
Cephalosporin	0.67 (0.51, 0.88)	317 (69.5)	673 (76.5)	.004
Carbapenem	0.64 (0.44, 0.95)	42 (9.2)	114 (13.0)	.03
Fluoroquinolone	1.07 (0.84, 1.36)	154 (33.8)	284 (32.3)	.60
Macrolide	1.06 (0.80, 1.40)	104 (22.8)	191 (21.7)	.70
Glycopeptide (Vancomycin)	0.94 (0.72, 1.21)	319 (70.0)	625 (71.0)	.63
Daptomycin/Linezolid (Other Anti-MRSA Drug)	0.60 (0.40, 0.89)	39 (8.6)	116 (13.2)	.01
Aminoglycoside	0.74 (0.54, 1.02)	69 (15.1)	169 (19.2)	.06
Metronidazole	0.83 (0.65, 1.05)	219 (48.0)	461 (52.4)	.12
Sulfa (Trimethoprim-Sulfamethoxazole)	0.82 (0.60, 1.11)	81 (17.8)	178 (20.2)	.20
Rifamycin	0.34 (0.18, 0.67)	13 (2.8)	61 (6.9)	.002
Topical Mupirocin	0.78 (0.44, 1.41)	22 (5.1)	48 (5.7)	.41
Intravenous or Oral Antifungal	0.71 (0.55, 0.92)	139 (30.5)	324 (36.8)	.01
H_2 Blocker	1.45 (0.99, 2.11)	409 (89.7)	761 (86.5)	.05
Proton Pump Inhibitor	0.65 (0.51, 0.83)	218 (47.8)	504 (57.3)	.0005
Vasopressor	0.95 (0.74, 1.22)	180 (39.5)	357 (40.6)	0.69

Note: Antibiotic use was determined within the past 6 months. H_2 blocker and proton pump inhibitor use were determined within the past 30 days. Vasopressor use was determined within the past 7 days.

3.2 MULTIVARIATE ANALYSIS

The final multivariate analysis model included 15 independently significant variables shown in Table 4. Seven factors were found to be positively associated with MRSA acquisition. and included a primary diagnosis of respiratory disease, digestive tract disease, or injury/trauma, any diagnosis of pneumonia, cerebrovascular/ peripheral vascular disease, intracranial ventricular shunt procedure, and a high risk unit

stay prior to index culture. Eight variables were found to be protective and included history of transplant, extracorporeal membrane oxygenation (ECMO), intravascular stenting/catheterization, and use of two beta lactam antibiotic classes (penicillin and cephalosporin), rifamycin, daptomycin/linezolid, and proton pump inhibitors. No interaction variables were found to be significant.

Table 4. Multivariate Model for Predicting MRSA Acquisition

Variable	**Odds Ratio (95% CIs)**	**p value**
Primary Diagnosis	-	.0119
Respiratory Disease vs. Circulatory Disease	1.81 (1.14, 2.88)	-
Digestive Tract Disease vs. Circulatory Disease	1.92 (1.12, 3.29)	-
Injury or Trauma vs. Circulatory Disease	1.94 (1.24, 3.06)	-
Other Diagnosis vs. Circulatory Disease[a]	1.28 (0.84, 1.96)	-
Pneumonia	1.76 (1.35, 2.30)	<.0001
Cerebrovascular or Peripheral Vascular Disease	1.53 (1.10, 2.12)	.0116
Intracranial Ventricular Shunt Procedure	2.11 (1.20, 3.72)	.0099
High Risk Unit Stay Prior to Index Culture	6.24 (2.12, 18.4)	.0009
History of Transplant	0.37 (0.22, 0.62)	.0001
Extracorporeal Membrane Oxygenation	0.47 (0.23, 0.94)	.0338
Intravascular Stent or Catheterization	0.58 (0.41, 0.82)	.0024
Penicillin Use	0.62 (0.48, 0.81)	.0055
Cephalosporin Use	0.64 (0.47, 0.86)	.0031
Daptomycin/Linezolid (Other Anti-MRSA Drug) Use	0.62 (0.40, 0.96)	.0306
Rifamycin Use	0.41 (0.20, 0.83)	.0133
Proton Pump Inhibitor Use	0.70 (0.53, 0.91)	.0089

Note: Comorbidities were present anytime during admission. Procedures were performed within the 30 days prior to acquisition of MRSA. Antibiotic use was determined within the past 6 months. Proton pump inhibitor use was determined within the past 30 days.
[a]This category had a CI that crossed 1.00 for but is kept in the model as part of a categorical variable.

For the subset of cases with cultures obtained only during a high risk unit stay, the final model included 11 significant variables. Only two variables, admission from a long-term care facility (aOR=2.19 (1.22, 3.92), p=.0082) and pneumonia (aOR=1.75 (1.29, 2.38), p=.0004) were associated with MRSA acquisition. Protective factors similar to those in the main model and with comparable aORs and p values (data not shown) included admission history of transplant, ECMO, intravascular stent or cardiac catheterization, and use of penicillin, cephalosporin, daptomycin/linezolid, and PPI. Additional protective factors identified included placement of an IABP or ventricular assist device (aOR=0.41 (0.20, 0.82), p=.0119) and carbapenem use (aOR=0.54 (0.33, 0.88), p=.0138).

The final model for the subset of cases identified only by nasal surveillance culture included 13 significant variables. Five factors were associated with MRSA acquisition and included admission from a long-term care facility (aOR=1.86 (1.04, 3.32), p=.0351), pneumonia (aOR=1.68 (0.44, 0.88), p=.0027), presence of an intracardiac pacemaker or defibrillator (aOR=1.96 (1.10, 3.50), p=.0229), tube feeding (aOR=1.46 (1.04, 2.06), p=.0308), and a high risk unit stay prior to index culture (aOR=4.62 (1.45, 14.78), p=.0098). Protective factors similar to those in the main model and with comparable aORs and p values (data not shown) included admission history of transplant, ECMO, intravascular stent or cardiac catheterization, and use of penicillin, cephalosporin, daptomycin/linezolid, and PPI. An additional protective factor identified was abnormal albumin (aOR=0.63 (0.45, 0.89), p=.0090).

4.0 DISCUSSION

4.1 EXPLANATION OF RESULTS

4.1.1 Overall findings

This case-control study identified several factors associated with MRSA acquisition among patients admitted to a high risk unit in a tertiary hospital setting, including a primary diagnosis category of respiratory disease, gastrointestinal disease, or trauma/injury, any diagnosis of pneumonia, cerebrovascular/peripheral vascular disease, exposure to a high risk unit, admission from a long-term care facility, intracranial ventricular shunt procedure, presence of an intracardiac pacemaker or defibrillator, and tube feeding. Protective factors identified that were similar across all sets of subjects analyzed included history of transplant, use of beta lactam antibiotics, daptomycin/linezolid, or PPI, ECMO, and intravascular stenting or catheterization.

In interpreting the results of these analyses, it is important to keep in mind the population studied, the setting, and the method for choosing the cases and controls. The population consists mostly of critically ill patients since the high risk units at UPMC PUH are comprised mainly of the ICUs. The number of comorbid illnesses and the severity of illness of the population are reflected in the adjusted Charlson Comorbidity Index, the number of abnormal laboratory values, and the mortality rates, which were not significantly different between the case and control groups. All the patients had at least one invasive procedure performed, and majority was on mechanical ventilation and at least one antibiotic. Thus, the lack of a particular risk factor such as a comorbid illness or a prior procedure did not mean that the patient had no risk factors but rather that the subject was exposed to a different comorbidity or procedure. The setting is also one where an intensive MRSA infection control bundle has been implemented and where the MRSA acquisition rates are quite low. The advantage of the study is in the large number of subjects and excellent medical records that could potentially identify risk factors for MRSA acquisition despite the baseline low MRSA acquisition rates reflective of a successful infection control strategy.

Since the cases and controls were matched by location and timing, it can be presumed that the two groups were exposed to similar group level antibiotic use or defined daily doses of antibiotics as well as a similar environment, so hospital level antibiotic use, MRSA colonization pressure, care workload, and unit location could not be studied as risk factors [14-15]. Since the groups were also matched by a minimum duration of stay, length of stay parameters would be reflective of the accuracy of the matching method and could not be studied as potential risk factors. Indeed, length of hospital stay, length of stay prior to the index culture, and lengths of stay in the high or non-high risk units were not associated with MRSA acquisition in this study. However, since cases potentially had their last negative nasal surveillance culture in a non-high risk unit and converted on their first day of admission to a high risk unit while some controls could have had their index culture on their first day of high risk unit admission, exposure to a high risk unit prior to index culture was able to be studied and found to be significantly different between the case and control groups. Likewise, exposure to a non-high risk unit was potentially different between the two groups if some subjects did not spend their entire stay in a high risk unit. The dichotomous variables indicating prior exposure to a high risk or non-high risk unit were thus included in the multivariate analysis. Since the subjects were all chosen based on cultures taken at a high risk unit, the resulting adjusted odds ratios (aOR) may not truly reflect the odds of exposure in a general population of MRSA converters to a certain type of unit.

4.1.2 Positively associated variables

The multivariate model identified a high risk unit stay prior to index culture as having the greatest association with MRSA conversion. This should be interpreted with caution since the absolute value of the aOR may not reflect the true odds of being exposed to a high risk unit among cases versus controls. However, since the high risk units were already historically determined to have higher MRSA infection rates compared to other nursing units, this finding is plausible. The ICUs may have had higher MRSA infection rates because of potential exposure to higher organism burden of MRSA as well as performance of more invasive procedures during a high risk unit stay.

Any diagnosis of pneumonia was significantly associated with MRSA acquisition in all the analyzed groups. This may reflect either an association with a diagnosis of pneumonia upon admission or association with hospital-acquired pneumonia. A diagnosis of pneumonia at any time is plausible as a risk factor for MRSA acquisition because of the decreased ability to clear secretions resulting in a favorable environment for MRSA to grow, damage to the respiratory tract as these conditions would promote adherence of MRSA, disruption of respiratory flora, and selective growth of MRSA due to antibiotic use.

Additionally, intubation and suctioning could serve as a portal of entry for the organism from the hands or equipment of the healthcare worker as could the exposure to other invasive procedures. This finding may be consistent with *S. aureus* preferring to colonize the nares and nasopharynx, which may be a source for aspiration and development of pneumonia. It may also reflect virulence factors in MRSA/*S. aureus* such adhesins, toxins, and phenol-soluble modulins that may be important in pneumonia pathogenesis [10, 33-34].

Primary diagnoses of respiratory disease, digestive tract disease, or injury/trauma diagnosis were associated with MRSA acquisition. This could be reflective of the underlying health status of the hosts or chronicity of illnesses in these diagnostic categories versus the reference category of circulatory illness or the mechanism of disease, such as the need for mechanical ventilation in complicated respiratory diseases. The types of procedures performed in patients with respiratory or gastrointestinal disease and the presence of open wounds in injury/trauma could increase the risk of MRSA acquisition. Among the comorbid illnesses (regardless of primary diagnosis), cerberovascular disease or peripheral vascular disease was found to be a risk factor. This variable includes patients with peripheral and cerebrovascular disease and so a subset also had chronic stasis ulcers and poor wound healing, which may put them at increased risk for MRSA acquisition. A subset of patients with cerebrovascular disease would also have undergone an intracranial ventricular shunt, which was the only procedure that was found to be significantly associated with MRSA acquisition. Ventricular shunts are often manipulated for drainage of cerebrospinal fluid multiple times a day, and this increased contact might explain the increased the risk of MRSA acquisition.

Admission from a long-term care facility was significant on subset analysis. Long-term care residents are often elderly, have multiple comorbidities, and are debilitated. Perhaps hospitalization unmasks previously undetected low level colonization as MRSA colonization can occur in as much as 62% of nursing home residents, whether nasally or extranasally, or the debilitation may contribute to increase risk of acquisition [35]. In addition, the presence of an intracardiac pacemaker or defibrillator and tube feeding was significant in the subset detected by nasal surveillance cultures only. These findings are consistent with conclusions from previously published studies and may be attributable to the presence of chronic foreign material that facilitate MRSA adhesion or manipulation and trauma of the upper nasopharyngeal passages which are the preferred site for colonization of *S. aureus* [10, 36]. The emergence of these risk factors in the subset analyses and not the main analysis may reflect the difference in the method of identification of the cases and controls in the subsets.

4.1.3 Negatively associated variables

A history of transplant appeared to be protective. This may be confounded by the antibiotics that the transplanted patients receive as the beta lactam antibiotic classes cephalosporin, penicillin, and carbapenem were shown to be protective. Of note, the transplant ICU MRSA acquisition rate per 1,000 patient days was the lower than any other high-risk unit (Table 5). Literature on group-level antibiotic use showed beta lactams to be a risk factor for MRSA colonization, which is contradictory to our findings, but this finding should be distinguished from being a risk factor for acquisition as opposed to just a finding of colonization [15-16]. Patient-level data in one study showed a trend for beta lactams towards being protective, which is more consistent with this study's results [15]. In multivariate analysis, rifamycin, daptomycin and linezolid use were also found to be protective. It is plausible that because these agents have activity against MRSA that MRSA growth on screening could have been suppressed. PPI were also found to be protective against MRSA acquisition, although this finding is difficult to explain in light of the association of PPI with the occurrence of pneumonia and other hospital-acquired pathogens such as *C. difficile* and gram positive coccal infections in a few studies [37-39]. One in vitro study actually investigates the potential use of PPI analogues as inhibitors of multidrug efflux mechanisms in *S. aureus*, which could point to a potential antibactericidal role [40].

Table 5. Distribution of Cases by Unit for 2007-2008 in Cases per 1,000 Patient Days

Unit Location	Patient Days	Total Number of Cases	Cases per 1,000 Patient Days
Medical ICU	23,385	50	2.1
Surgical ICU	5,100	7	1.4
Trauma ICU	15,441	35	2.3
Transplant ICU	18,899	21	1.1
Neurosurgical and Neurology ICU	20,963	42	2.0
Cardiothoracic ICU	14,603	24	1.6
Coronary Care Unit	7,008	15	2.1
Orthopedic Unit	11,454	21	1.8

Cardiology procedures such as extracorporeal membrane oxygenation, cardiac catheterization and stenting, the placement of an IABP or ventricular assist device, were found to be protective in all the multivariate models. The trend throughout the study's results indicates that there were more cardiovascular procedures or diagnoses among the controls. This finding may be reflective of the underlying good health status of subjects who undergo some of these procedures, as they are often only

performed in patients who receive medical clearance or in those with an acute onset cardiovascular event. Of note, no interaction or association with mupirocin, which is often used for nasal decolonization, or other antibiotics were noted.

4.1.4 Variables not associated with MRSA acquisition

There was no association between isolation precautions for other organisms and MRSA acquisition. Contact precautions are designed to prevent transmission from the isolated case to others, not from others to the individual and so barrier use in cases would not be expected to be protected. No interaction variables were found to be significant. Certain patient-associated risk factors identified in previous studies were not found to be significant in this study, such as tracheostomy, skin ulcers, and fluoroquinolones, although the unadjusted mORs for these variables trended towards an association with MRSA acquisition. The smaller subsets analyzed showed some similarities in results to the larger dataset, although the smaller sample size in these subsets may explain the lack of significant association found in some of the variables in the original final model.

4.2 LIMITATIONS

One limitation of the study is that data was retrospective and only captured via electronic extraction. Therefore, certain conditions, such as skin ulcers, may have been missed if they were not coded into ICD9 codes. Another limitation is that there may not always be culture confirmation of MRSA acquisition if cultures were not ordered on patients or if cultures were done at another laboratory. Completeness of individual subject data depended on the available electronic and paper records. Sensitivity of detection of MRSA also depended on the sensitivity of the culture methods. However, these potential biases would unlikely be different for the groups. Due to multiple comparisons among many variables, the p value of <0.05 may be overly sensitive to detect potential risk factors for MRSA acquisition but was felt to be appropriate due to the exploratory nature of the study. Because of the study design, residual confounding may have occurred. In addition, causation cannot be determined in an observational study.

5.0 CLINICAL SIGNIFICANCE AND CONCLUSION

The final model included 15 independently significant variables. Seven factors were found to be positively associated with MRSA acquisition. They included a primary diagnosis of respiratory disease digestive tract disease, or injury/trauma, any diagnosis of pneumonia, cerebrovascular/ peripheral vascular disease, intracranial ventricular shunt procedure, and a high risk unit stay prior to index culture. As 3 of the 7 factors that were positively associated with MRSA acquisition were primary diagnoses present on admission, they were not modifiable. Of the remaining 4, pneumonia, specifically pneumococcal pneumonia, could potentially be reduced by maintaining high compliance with pneumococcal vaccine immunization but this too would likely need to occur prior to admission. The other conditions found to be associated with MRSA acquisition could potentially be targeted for more intensive surveillance in hopes of identifying (and isolating) acquisition sooner. Admission to a high risk unit in itself is not modifiable.

Eight variables were found to be protective and included two beta lactam antibiotic classes (penicillin and cephalosporin), rifamycin, daptomycin/ linezolid, proton pump inhibitors, history of transplant, extracorporeal membrane oxygenation (ECMO), and intravascular stenting/catheterization.

Overall, there was a remarkable paucity of significance of many of the major surgeries and procedures studied as risk factors for MRSA acquisition. This argues for the importance of the rigorous application of routine infection control infection control strategies such as hand hygiene before and after patient and or environmental contact, habitual cleaning of equipment, as well as assiduous use of and removal of barriers as appropriate. Additionally, the use of the MRSA prevention bundle may have helped to safeguard patients undergoing procedures, who might not have otherwise been protected, as this program identifies colonized patients and requires implementation of barrier precautions.

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