Mortality among methicillin-resistant *Staphylococcus aureus* carriers in long-term care facilities

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ABSTRACT

Introduction. Little is known about the natural course of patients with chronic stable illnesses colonized with methicillin-resistant *Staphylococcus aureus* (MRSA). The aim is to determine the impact of MRSA colonization in mortality among long-term health care facility (LTHCF) residents.

Method. A multicenter, prospective, observational study was designed. Residents in 4 LTHCFs were classified according to MRSA carriage status and followed for 12 months. Treatment consisted of 5 days of nasal mupirocin in MRSA carriers.

Results. Ninety-three MRSA-carriers among 413 residents were identified. Thirty-one MRSA-colonized patients died during the study period, 11 of whom from an infectious disease. Independent predictors of their higher mortality rates included heart failure, current neoplasm, MRSA carriage and COPD at 3 months and these same factors plus stroke, Barthel index <40, pressure ulcers, and older age at 12 months. MRSA-persistence was 35% and 62.5% at 3 and 12 months, respectively.

Conclusions. MRSA colonization among frail LTHCFs residents is highly prevalent, and is associated with higher mortality. Despite treatment of MRSA carriers, many remained colonized. Factors that promote persistence of MRSA colonization, and the impact of their modification on mortality rates in these patients, need further investigation.

Key words: Mortality. Nursing homes. Methicillin-Resistant *Staphylococus aureus*.

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Mortalidad entre los portadores de *Staphylococcus aureus* resistente a la meticilina en centros sociosanitarios

RESUMEN

Introducción. La evolución natural de los pacientes con enfermedades crónicas y estables que son colonizados con *Staphylococcus aureus* resistente a la meticilina (SARM) es poco conocida. El objetivo es determinar el impacto de la colonización por SARM en la mortalidad entre los residentes de centros sociosanitarios (CSS).

Métodos. Se diseñó un estudio multicéntrico, prospectivo y observacional. Los residentes de 4 CSS tras ser clasificados según su estado de portador de SARM, fueron sometidos a seguimiento durante 12 meses. Los portadores fueron tratados 5 días con mupirocina nasal.

Resultados. Entre 413 residentes se identificaron 93 portadores. Durante el período de estudio murieron 31 colonizados, 11 de los cuales por infección. Predictores independientes de mortalidad incluyeron, a los 3 meses: insuficiencia cardíaca, neoplasia activa, colonización por SARM y enfermedad pulmonar obstructiva crónica; a los 12 meses incluyeron estos mismos factores y además: ictus, índice de Barthel <40, úlceras de presión, y edad más avanzada. La persistencia de SARM fue 35% y 62,5% a los 3 y 12 meses, respectivamente.

Conclusiones. La colonización por SARM entre los pacientes frágiles ingresados en CSS tiene una elevada prevalencia, y se ha asociado a mayor mortalidad. A pesar del tratamiento de los portadores, muchos permanecieron colonizados. Es necesario investigar mejor los factores que favorecen la persistencia de colonización por SARM, y el impacto de su modificación sobre las tasas de mortalidad en estos pacientes.

Palabras clave: Mortalidad. Centros sociosanitarios. *Staphylococus aureus* resistente a la meticilina.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection has been shown to increase morbimortality and healthcare costs as compared to other infections[1]. Data to support the previous statement come primarily from studies evaluating acute patients admitted to high-technology hospitals[2]. MRSA infection itself, however, has not been undoubtedly linked to the excess mortality across all studies[3], as empirical treatments are frequently ineffective for this condition[2,4,5] and MRSA carriers exhibit frequent and severe comorbidities.

Current knowledge about the MRSA carrier state, irrespective of the patients' infection status, is scarce. Studying the evolution of MRSA-colonized patients in long-term care facilities may provide an accurate view of the significance of MRSA colonization, and help disentangle it from other short-term life expectancy predictors in acute patients. With this aim, we analyzed the 3-month and 1-year mortality in a cohort of MRSA colonized patients admitted to various long-term care facilities in a health region with a single acute-care reference hospital.

METHODS

During the month of December 2003 an epidemiological survey was carried out and samples for microbiological analysis were collected from all the patients admitted to any of 4 long-term health care facilities (LTHCF) in a single health region. MRSA carriers were evaluated clinically and microbiologically every 3 months for a year or to the time of their decease, whichever occurred first. These 4 LTCHF provide health care to a population of about 220,000 and share a common acute-care reference hospital. Each one of the centres (henceforth termed A, B, C, and D) provides a combination of long-term acute, rehabilitation and palliative care.

This work was approved by the reference Ethical Committee and every patient (or a qualified proxy) gave his or her consent. MRSA detection was performed on swabs taken from the nasal fossae and any cutaneous ulcer participants were found to have. Samples were collected by designated members of the nursing staff in each centre using a swab that was subsequently introduced in a pipe filled with transport medium and sent to the microbiology laboratory of the reference hospital. All samples were cultured on standard media, including the Columbia blood-agar and the antibiotic supplemented Columbia blood-agar (Columbia CNA agar) bases. *Staphylococcus aureus* was identified by the results of a gram stain and the catalase and coagulase tests; a disc diffusion antibiogram was performed and interpreted according to NCCLS standards[6].

The date of decease of each participant was recorded. The cause of death was classified as "infectious" if it had been suspected as such (regardless of whether it had been microbiologically proven or not), or as "not infectious" (any other or unknown causes).

The epidemiological survey to evaluate risk and persistence factors for MARSA colonization was performed through personal interview and/or review of the medical records of each inpatient, and included: personal information, past medical history, clinical assessment of cognitive function, performance status and degree of dependence (expressed according to the Barthel index (BI)), nutritional assessment with the short form of the Mini Nutritional Assessment (SF-MNA), antibiotic or steroid treatment in the preceding 6 or chemotherapy in the previous 3 months, neutrophil count <500 cells/mL, skin lesions, any invasive procedure (including indwelling urinary, enteral or vascular catheters, parenteral nutrition, non-invasive mechanical ventilation, with mention of their date if insertion/initiation and duration) and surgical drainage procedures. Basic laboratory results for each patient were also recorded.

A 2% mupirocin in a paraffin base was applied to the inner surface of each nostril three times daily for 5 days in every patient recognized as being MRSA-colonized. Eradication of colonization in other locations was not attempted, although all skin ulcers were kept thoroughly cleansed.

A post-hoc analysis of mortality associated to the MRSA-carrier state in patients who resided in a LTHCF at the beginning of the study, compared survivors to those who died during the follow-up period. Statistical analysis consisted in the comparison of survival curves of MRSA-carriers and non-carriers, and the assessment of risk factors for mortality at 3 and 12 months using contingency tables and, the t-Student or U-Mann-Whitney tests. Finally the analysis of independent predictors of mortality was performed entering those factors associated with mortality in a bivariate analysis, in a multivariate logistic regression model.

RESULTS

A total of 413 patients admitted in one of the LTHCFs at the beginning of the study period were included in the analysis. Ninety-three (22.5%) were identified as MRSA-carriers. The microorganism was isolated from the nares in 57 patients (61.3% of carriers), from the nares and skin ulcers in 14 (15.1%) and from only ulcers in 22 (23.7%). The distribution of MRSA-carriers between the various centres was 35.5% (centre A), 25.8% (B), 21.5% (C) and 17.2% (D), which corresponded to a prevalence of MRSA carriage of 15.8%, 20.5%, 24.4% and 29.2%, respectively (p=0.116).

The epidemiological and clinical features of MRSA-carriers and non-colonized patients are shown in table 1. Our study disclosed statistically significant differences regarding variables that have been classically associated to the MRSA carrier state, such as skin lesions, decubitus ulcers, urinary catheters and a greater degree of functional dependence (BI lower than 40).

The overall mortality rate at 12 months was 22% (90 patients). MRSA-carriers had a greater mortality rate, both at 3 months (OR 3.18; 95% CI 1.54-6.60) and at 12 months (OR 2.21; 95% CI 1.32-3.70), as shown in the figure 1 (long rank test: p<.001) tables 1 and 2.

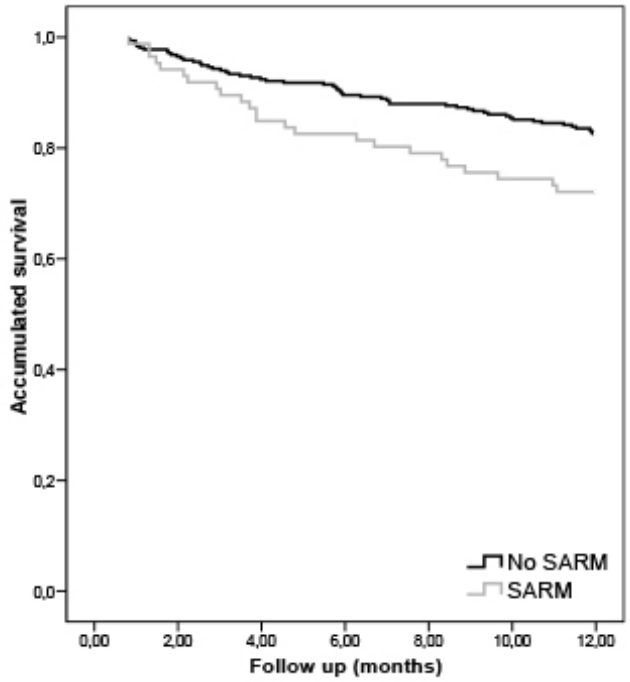

Figure 1 | **Survival curves. MRSA(+) vs. MRSA(-) in residents of Long-term Health Care Facilities. Long rank test: p< 0.001, both at 3 and 12 months.**

Patients MRSA+ in grey versus patients MRSA- in black

Thirty-five percent of all patients who had been found to be MRSA-carriers at the beginning of the study period were found to be colonized at 3 months; at 6 and 9 months the proportion of patients who were colonized rose to 47% and 46%, respectively. Only 56 patients could be evaluated with nares and ulcer samples at the end of the 12 month follow-up, and at that time point, 35 patients (62.5%) were MRSA-carriers.

Table 2 displays the factors that were found to be associated to mortality among patients admitted to LTHCFs at 3 and 12 months. Four individuals were known to have died during the study period, but they had to be excluded from analysis at 3 months, because their date of decease was not known. The independent predictors of mortality that were identified by the multivariate analysis included heart failure (OR 4.6; 95% CI 1.7-12.4), current neoplasm (OR 4.56; 95% CI 1.6-13.2), MRSA carriage (OR 3.41; 95% CI 1.3-8.9) and COPD (OR 2.79; 95% CI 1.1-7.3) at 3 months, and current neoplasm (OR 19.48; 95% CI 7.1-53.1), heart failure (OR 3.01; 95% CI 1.4-6.3), MRSA carriage (OR 2.91; 95% CI 1.2-6.8), COPD (OR 2.13; 95% CI 1.0-4.6), stroke (OR 2.80; 95% CI 1.3-6.1), BI<40 (OR 3.38; 95% CI 1.6-7.2), pressure ulcers (OR 3.40; 95% CI 1.3-9.3), and older age (OR 1.39; 95% CI 1.0-1.1) at 12 months. Urinary catheters were associated with a lower mortality rate (OR 0.14; 95% CI 0.0-0.7). The model did not include steroid treatment, as its association to COPD could mask the results.

The cause of death of the 31 deceased MRSA-colonized patients was considered to be infection in 11 cases (4 with infection of the skin ulcers, 6 with respiratory infection, and 1 with urinary tract infection) and not infectious in the remaining 20 (6 progression of the current neoplasm, 4 heart failure, 2 rectorrhagia, 2 ischemic heart disease, 1 hypercapnic respiratory failure, 1 deep venous thrombosis, 1 peripheral arterial ischemia, and 3 unknown).

DISCUSSION

This observational study confirms there is a high prevalence of MRSA colonization among patients with pluripathology who are admitted to LTHCFs for long time periods[7,8] and this colonization has prognostic relevance. Several patient-related factors, such as the existence of vascular or pressure ulcers, and institution-related factors, such as infrastructure and organization charts, determine the observed rates of MRSA colonization in medical centers[9-11]. These aspects have been previously evaluated in other studies covering risk and persistence factors for MRSA in different groups[12,13], Bloemendaal et al. studied the transmission and colonization persistence of *S. aureus* comparing methicillin-resistant to methicillin-sensible strains, and detected a more stable nasal colonization by MRSA[14]. Several authors emphasize the importance of mathematical models to investigate transmission dynamics in nursing homes where MRSA is highly endemic[13]. Further studies are needed involving nursing home residents and health care workers. The collaboration between different health institutions is also important in MRSA spread control[13,15].

The most significant finding in this study is the high mortality rate observed both in the short and intermediate terms among MRSA carriers as compared to non-carriers. The correlation observed with MRSA carriers and mortality is independently of other known factors associated with mortality in these colonized and institutionalized patients. Moreover, it should be stressed that this applies mainly to chronically ill patients who are merely colonized, and not to acutely ill patients with active infections that adversely impact their short term prognosis. One out of 6 patients died within 3 months, and 1 in 3 did within 12 months of detecting the MRSA colonization, rates which are three times higher than those of non-colonized patients in our sample. Other analyzed variables, such as various comorbidities and functional status, are also predictors of death among institutionalized patients. Nevertheless, among MRSA carriers, the relative risk of dying within 3 or 12 months was unchanged after adjusting for these co-variables using the Mantel-Haenszel stratified analysis.

A higher mortality rate among MRSA colonized patients in LTHCFs has been reported[7,9,10,16,17], but a comprehensive explanation for this association has not been provided. In contrast, some authors found no relationship between MRSA colonization and mortality[18-20]. This lack of association has been accounted for by different factors. On one hand, the elderly living in a nursing home have prominent comorbidities and may require frequent admissions to acute care hospitals. Both the need for readmission to acute care hospitals and the progression of functional

Table 1 **Differential clinical and epidemiological characteristics of patients.**

	MRSA (N=93)	Non MRSA (N=320)	p
Female, n (%)	57 (61.3)	205 (64.1)	0.625
Age (years)	76.7±11.5	76.6±13.3	0.738
Diabetes mellitus, n (%)	27 (29.0)	75 (23.4)	0.326
Heart failure, n (%)	28 (30.1)	80 (25.0)	0.366
Stroke, n (%)	21 (22.6)	82 (25.6)	0.474
COPD, n (%)	22 (23.7)	54 (16.9)	0.167
Arterial insufficiency, n (%)	16 (17.2)	40 (12.5)	0.285
Venous insufficiency, n (%)	17 (18.3)	74 (23.1)	0.279
Current neoplasm, n (%)	11 (11.8)	35 (10.9)	0.834
Liver cirrhosis, n (%)	4 (4.3)	10 (3.1)	0.533
Chronic renal failure, n (%)	1 (1.1)	11 (3.4)	0,310
Other comorbidities, n (%)	42 (45.2)	103 (32.2)	0.042
Cognitive impairment, n (%)	51 (54.8)	162 (50.6)	0.632
BI<40, n (%)	54 (58.1)	146 (45.6)	0.031
Possible malnutrition (SF-MNA<11) n (%)	56 (60.2)	231 (72.2)	0.537
Albumin g/L	38.0±43.3	32.5±5.4	0.204
Neutrophil count (cells/mL)	7,953.2±3,197.3	7,403.3±3,069.5	0.097
Neutrophil count <=500 cells/mL, n (%)	35 (37.6)	117 (36.6)	0.833
Total leukocyte count	7,953.2±3,197.3	7,403.3±3,069.5	0.097
Lymphocyte count	2,045.0±2,197.1	2,016.5±1,713.1	0.442
Skin lesions (other than ulcers), n (%)	16 (17.2)	18 (5.6)	<0.001
Ulcers, n (%)	30 (32.3)	32 (10.0)	<0.001
Urinary catheter, n (%)	16 (17.2)	9 (2.8)	<0.001
Corticosteroid therapy (latest 6 months) n (%)	13 (14.0)	42 (13.1)	0.836
Chemotherapy (latest 3 months), n (%)	1 (1.1)	3 (0.9)	1
Mortality at 3 months, n (%)	15 (16.1)	18 (5.6)	0.001
Mortality at 12 months, n (%)	31 (33.3)	59 (18.4)	0.002

COPD Chronic Obstructive Pulmonary Disease. BI Barthel index[a]. SF-MNA short form of the mini nutritional assessment scale[b]. g/L grams per liter. cells/mL cell count per milliliter.

[a]BI score interpretation: <20 total dependence, 20-60 severe dependence, 65-90 moderate dependence, 95 slight dependence, 100 independence.

[b]SF-MNA score interpretation: <11 at risk for undernutrition, > or = 11: acceptable nutritional status.

status index scores have been studied, but no relationship to the mortality rates has been disclosed[16]. On the other hand, they have more antibiotic pressure and frequent contacts with other residents or caregivers among which MRSA prevalence is high. Robust conclusions regarding the role of MRSA colonization among nursing home residents, however, are not available as studies in this field are scarce and have conflicting results[12,19,21].

The evaluation of the causes of death that we retrospectively performed suggests that most patients did not die from MRSA infection. Out of the 31 deceased patients, there was a suspicion of active infection in only 11 (35.5%). The microbiological etiology in these cases, however, could not be determined, as they died in a LTHCF where cultures are not readily performed[22]. However we cannot exclude MRSA as a direct cause of death in them, mainly from skin infections.

Several authors and consensus statements[11] advocate for a proactive detection of MRSA in LTHCFs, and the implementation of isolation procedures in an attempt to reduce the colonization and infection rates. Other documents[15,23] preconize more general measures in LTHCFs, because, despite high prevalence of MRSA colonization, the risk of developing an active infection is considered to be low[18,24]. Our observational study does not provide additional data to solve this dilemma, as only the higher mortality among MRSA carriers can be clearly deduced from our results.

A limitation in our study is the fact that MRSA was not systematically investigated in the perineum and the pharynx, and this may have underestimated the proportion of colonized residents. Moreover, the possibility of de novo colonization of patients found to be not colonized at the beginning of the study period was also not evaluated.

Another potential limitation of our study design is the fact that no information on the time span from colonization to decease was available, because the initial evaluation was a prevalence survey (all participants were evaluated simultaneously) and not performed at the time of their admission to the LTHCF. This design allows for the detection of increased mortality rates, but not for variations in this measure with regard to the duration of the colonization.

It would be interesting to identify which factors promote persistence of MRSA colonization, and attempt to modify them, if possible, to determine whether this approach could modify mortality in this group of patients. Most MRSA positive patients in our study remained colonized during the follow-up period, despite the fact that all of them had been treated with topical mupirocin. Once colonized, nursing home residents usually remain colonized with the same MRSA strain, at least for 1 year[25,26]. In this study, colonized individuals were evaluated every 3 months for a year or until their death, and of the 56 MRSA-positive patients who were alive and could be contacted for control at 12 months, 35 (62.5%) remained positive.

It is well known that mupirocin has a low success rate in eradicating MRSA colonization, Strausbaugh et al. found that

Table 2 **Baseline factors associated with mortality at 3 and 12 months in a cohort of residents of chronic care facilities.**

	Baseline factor	Alive	Dead	p	OR	95%CI
At 3 months		376	33			
N=409	Heart failure, n (%)	91 (24.2)	15 (45.5)	0.005	2.81	1.34-5.91
4 missing	COPD, n (%)	61 (16.2)	15 (45.5)	<0.001	4.40	2.08-2.28
	Current neoplasm, n (%)	35 (9.3)	11 (33.3)	<0.001	4.70	2.11-10.5
	BI<40, n (%)	174 (46,3)	22 (66.7)	0.027	2.29	1.08-4.85
	Ulcers, n (%)	52 (13.8)	10 (30.3)	0.013	2.66	1.20-5.91
	Urinary catheter, n (%)	20 (5.3)	5 (15.2)	0.043	3.13	1.09-8.98
	MRSA carriage, n (%)	78 (20.7)	15 (45.5)	0.001	3.18	1.54-6.60
	Albumin (g/L)	34.4±23.1	28.1±4.3	<0.001	-	-
	Lymphocyte count (cells/mL)	2,077±1,833	1,024±371	0.041	-	-
At 12 months		323	90			
N=413	Heart failure, n (%)	72 (22.0)	36 (38.9)	0.001	2.30	1.39-3.79
	Stroke, n (%)	74 (22.9)	29 (32.2)	0.077	1.59	0.95-2.66
	COPD, n (%)	47 (14.6)	29 (32.2)	<0.001	2.73	1.59-4.68
	Arterial insufficiency, n (%)	37 (11.5)	19 (21.1)	0.020	2.05	1.11-3.78
	Current neoplasm, n (%)	19 (5.9)	27 (30.0)	<0.001	6.59	3.45-12.6
	Possible malnutrition (SF-MNA≤11), n (%)	223 (69.0)	64 (71.1)	0.012	4.21	1.27-14.0
	BI<40, n (%)	140 (42.7)	60 (64.4)	<0.001	2.68	1.63-4.39
	Ulcers, n (%)	36 (11.1)	26 (28.9)	<0.001	3.17	1.79-5.62
	Urinary catheter, n (%)	15 (4.6)	10 (11.1)	0.026	2.53	1.09-5.83
	MRSA carriage, n (%)	62 (19.2)	31 (34.4)	0.002	2.21	1.32-3.70
	Age (years)	75.8±13.5	79.6±10.1	0.031	-	-
	Albumin (g/L)	32.8±5.2	37.1±43.5	0.006	-	-

COPD Chronic Obstructive Pulmonary Disease. BI Barthel index[a]. SF-MNA short form of the mini nutritional assessment scale[b]. g/L grams per liter. cells/mL cell count per milliliter. OR Odds Ratio. CI Confidence Interval.
[a]BI score interpretation: <20 total dependence, 20-60 severe dependence, 65-90 moderate dependence, 95 slight dependence, 100 independence.
[b]SF-MNA score interpretation: <11 at risk for undernutrition, > or = 11: acceptable nutritional status. Bivariate analysis, in a multivariate logistic regression model.

MRSA colonization could be eradicated in 43% of nursing home residents, but persistence of eradication was assessed for only one month[27]. In a similar way Mody et al. observed MRSA decolonization for up to 6 months, although this did not reach statistical significance and 14 patients in their sample relapsed and became chronic MRSA carriers[28]. In this setting, attempts to decolonize affected individuals may need to be aimed at the detection and control of any modifiable persistence factors for this condition.

Many individuals carry *S. aureus* in their nares for long periods of time and never develop infections. However, a high risk of infection exists when these patients undergo invasive procedures, after an aspiration event, a breach in the skin or a bladder obstruction. Drinka et al, observed 1.6 episodes of infection per 100 residents per year in a veterans home[12]. This low figure may well be an underestimation, as it relies on a retrospective observation and cultures were not routinely performed[29]. Other authors have also reported low MRSA infection rates in LTHCF[30], although their data should be cautiously interpreted because asymptomatic carrier rates likely vary between different institutions.

In summary, nasal carriage of MRSA in LTHCF was independently associated with higher mortality rates. This observation is in accordance with previously published data[9]. Further studies are needed to determine whether interventions on modifiable persistence factors for MRSA could counterbalance the increased mortality rate in colonized patients over the short and intermediate terms.

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CONFLICT OF INTEREST

There is no conflict of interest in this study, including finantial, personal or any other potential conflict.

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