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Risk factors for methicillin-resistant *Staphylococcus aureus* colonisation or infection in intensive care units and their reliability for predicting MRSA on ICU admission

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SUMMARY

Predicting methicillin-resistant *Staphylococcus aureus* (MRSA) in intensive care units (ICUs) avoids inappropriate antimicrobial empirical treatment and enhances infection control. We describe risk factors for colonisation/infection related to MRSA (MRSA-C/I) in critically ill patients once in the ICU and on ICU admission, and search for an easy-to-use predictive model for MRSA colonisation/infection on ICU admission. This multicentre cohort study included 69,894 patients admitted consecutively (stay >24 h) in April-June in the five-year period 2006-2010 from 147 Spanish ICUs participating in the National Surveillance Study of Nosocomial Infections in ICUs (ENVIN-HELICS). Data from all patients included were used to identify risk factors for MRSA-C/I during ICU stays, from admission to discharge, using uni- and multivariable analysis (Poisson regression) to check that the sample to be used to develop the predictive models was representative of standard critical care population. To identify risk factors for MRSA-C/I on ICU admission and to develop prediction models, multivariable logistic regression analysis were then performed only on those admitted in 2010 (n=16950, 2/3 for analysis and 1/3 for subsequent validation).

We found that, in the period 2006-2010, 1046 patients were MRSA-C/I. Independent risk factors for MRSA-C/I in ICU were: age >65, trauma or medical patient, high APACHE-II score, admitted from a long-term care facility, urinary catheter, previous antibiotic treatment and skin-soft tissue or post-surgical superficial skin infections. Colonisation with several different MDRs significantly increased the risk of MRSA-C/I. Risk factors on ICU admission were: male gender, trauma critical patient, urgent surgery, admitted from other ICUs, hospital ward or long-term facility, immunosuppression and skin-soft tissue infection. Although the best model to identify carriers of MRSA had a good discrimination (AUC-ROC, 0.77; 95%CI, 0.72-0.82), sensitivity was 67% and specificity 76.5%. Including more complex variables did not improve prediction capability. Our conclusion is that clinical-demographic risk factors for colonisation/infection related to MRSA should not be used to accurately identify patients who would benefit from empirical anti-MRSA treatment or from specific preventive measures. Independent risk factors for MRSA colonisation/infection during ICU stay and on ICU admission are described. The latter should be considered in future studies for MRSA prediction.

Keywords: prediction model, intensive care, methicillin-resistant *Staphylococcus aureus*, risk factors.

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INTRODUCTION

Impact on global mortality associated with invasive infections of methicillin-resistant *Staphylococcus aureus* (MRSA) has been estimated at 20% [1-4]. Each MRSA infection generates a 9-day increase in hospital stays and an estimated cost of 27,000 US-dollars (380 million Euros each year in Europe) [5, 6].

MRSA detection on admission to the Intensive Care Unit (ICU) is crucial, not only to avoid inappropriate empirical treatment, but also in terms of infection control [7]. It is on this last point in particular which a lot of discussion still exists. Although most experts recommend the adoption of active surveillance against MRSA in high risk places or situations like ICU or outbreaks, cost-effectiveness, consumption of laboratory resources or the negative effects that strict isolation have over ICU patients make us conservative in adopting those recommendations [8-10].

Moreover, most scientific societies endorse active surveillance in critical care patients, recommending universal screening and shortening overall isolation time [11, 12]. Nevertheless, studies in which the benefit of a surveillance program seems to be clear contrast with others like the STAR-UCI or the REDUCE-MRSA, in which the contrary is shown, sustaining that in routine ICU practice, universal decolonization is more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates [13-17].

On ICU admission, it is estimated that 5-15% of the patients are colonized by MRSA and those previously colonized present a 8-fold increase in the risk of MRSA infection, an event that occurs in nearly 25% of those patients [18, 19]. A method needs to be developed that appropriately discriminates those patients colonized/infected by MRSA (MRSA-C/I) on ICU admission. An alternative approach to universal decolonization is the development of predictive models based on clinical-demographic risk factors, especially those easy-to-know on admission, and not depending on clinical records which are not always available.

Thus, this study has one main objective: to identify those easy-to-know risk factors on ICU admission associated with colonisation or infection by MRSA, and determine the reliability of a predictive model to detect patients with high probability of being MRSA-C/I on ICU admission. To ensure that the sample we are working with is representative of standard critical care population we also study and describe the main risk factors associated with MRSA-C/I in critical patients during ICU stay.

PATIENTS AND METHODS

The *Estudio Nacional de Vigilancia de Infecciones Nosocomiales en Unidades de Cuidados Intensivos* (National Surveillance Study of Nosocomial Infections in Intensive Care Units, ENVIN) registry was created in 1994 and has collaborated from its inception with the European registry "Hospitals in Europe Link for Infection Control through Surveillance" (HELICS). This multi-center prospective data collection system is designed to record infections related to invasive devices developed during ICU stay. The participating ICUs are uniformly distributed throughout the country, and 87.1% are combined medical-surgical units. Data are collected using the ENVIN-HELICS software application located in a web-based server. The database (in SQL server) runs on the same server. Data is collected by the critical infection expert in each ICU. ENVIN-HELICS registry has been audited, showing that there was good correlation between data reported by the registrars and data validated by auditors, confirming its reliability [20].

The present study includes information collected prospectively, from admission to discharge, from ICU of all patients admitted consecutively (and with at least 24 h of stay) in the 147 participating Spanish ICUs, in the months of April, May and June during the period 2006-2010. Patients are followed-up until discharge from ICU or to a maximum of 30 days in the unit.

The primary outcome of interest was colonisation or infection by MRSA, either on admission or during ICU stay. After the detection of oxacillin/methicillin resistance by any specific laboratory test and in any sample, critical care physician in charge of the patient or the ENVIN-UCI registrars or auditors estimates if it corresponds to a MRSA Colonisation or Infection, either ICU-related (device-related infection acquired during their ICU stay, secondary bloodstream infection, intubation-associated pneumonia and urethral catheter-related urinary infection) or not (CDC crite-

ria). In 2010 we differentiated between previous (when identified before or during the first 48h of ICU stay) or during ICU stay.

"MRSA on admission" was defined as being colonized or infected by MRSA before or not later than 48 hours after ICU admission. Apart from MRSA, other multidrug resistant organisms (MDRO) analyzed were *Pseudomonas aeruginosa* resistant to three or more antipseudomonal antibacterials families, extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae*, carbapenem-resistant *Acinetobacter* or vancomycin-resistant *Enterococcus* (VRE). All variable definitions can be found in the ENVIN reference manual (available on http://hws.vhebron.net/envin-helics/).

There was no uniform method for screening and identifying MRSA patients, as it depends on each ICU surveillance policy and the hospital Microbiology Laboratory resources.

This study was approved by the hospital reference Institutional Review Board/Ethics Committee and the ENVIN Steering Committee.

Continuous variables are described as mean and standard deviation (SD), or as median and inter-quartile range, if they showed a skewed (asymmetric) distribution. Categorical variables are described with absolute frequencies and percentages. Incidence was defined as number of C/I by MRSA per 100 patients admitted to ICU. Comparison of demographic and clinical characteristics of C/I and non-C/I by MRSA was made using the Student *t*-test (for continuous variables with normal distribution) and the Pearson χ^2 test (for categorical variables).

We divided the study in two parts. In the first one we checked the appropriateness of the sample from which the predictive models were going to be developed, identifying independent risk factors associated with MRSA-C/I either on admission or during ICU stay. Univariate analysis and multivariate Poisson regression was performed on variables from the entire patient population (n=69894, 2006-2010), as we have length of stay in ICU available.

In the second part we concentrated on ICU admission. Our aim was not only to identify independent risk factors but also to create a simple prediction rule based on a limited number of easy-to-know risk factors, being aware that some studies show no significant differences in terms of prediction capacity if we eliminate some risk factors from complex prediction models to make them easier to use [21-23]. For the identification of the risk factors and for the development of the predictive models we used only the 16950 patients admitted in 2010, as it was only from 2010 when the registry distinguishes between MRSA-C/I prior or during ICU stay. Among those patients, two groups were chosen by simple random sampling, 2/3 for analysis and development of the model (with a multivariate logistic regression analysis) and 1/3 for validation. Among all variables studied, we chose only those which can be easily identified by clinicians, without requiring clinical records or even patients collaboration. Those easy-to-know variables that correspond to risk factors with clinical plausibility and a clear association in the univariable analysis ($P<0.05$) were included in the multivariate analysis. The logistic regression model was fitted including all associated variables (*P* value less than 0.05), eliminating any variable if the chi-square statistic of the likelihood ratio test indicated no statistical significance ($P<0.05$), and no substantial impact in odds ratio estimation was observed. The results of the multivariate models are expressed as odds ratio (OR) with 95% confidence interval and *P*-values.

Finally, validation of the model was managed as follows: calibration was tested using the Hosmer-Lemeshow goodness-of-fit test, the significance level was defined as $P<0.05$ and discrimination was evaluated with the area under ROC curve (AUC-ROC), as a measure of the predictive power of the model.

Data were analyzed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA) and Stata software, version 9.2 (StataCorp, College Station, TX).

RESULTS

In our study, 69894 patients were included (11684, 12453, 13824, 14983 and 16950 for the years 2006, 2007, 2008, 2009 and 2010, respectively). MRSA was detected in 1046 patients during the 5 years of the study and in 258 in 2010, with a stable incidence density rate of 2.7 for 2006, 1.8 for 2007, 2.1 for 2008, 2.1 for 2009, and 2.3 for 2010. Among all *S. aureus* isolated in critical patients that year, MRSA strains were 21.8%. On ICU admission, the prevalence was 0.8% in 2010.

The results of the multivariate Poisson regression model are shown in Table 1. Several variables emerged as independent risk factors for MRSA-C/I in ICU (either on admission or during ICU stay): age >65, trauma or medical patients, severity based on APACHE II scale, admitted from a long-term care facility, urinary catheter, previous antibiotic treatment, and patients with skin-soft tissue or post-surgical superficial skin infections. Female gender and immunodeficiency emerged as protective factors. Multi-colonisation (by MRSA and other MDRO) is frequent and significantly increases the risk of being MRSA-C/I.
With respect to the main objective. The multivariate logistic regression model identified some risk factors that were independently associated with MRSA on ICU admission (Table 2). Of the variables entered in the first step (age, sex, type of patient, urgent surgery, origin, immunosuppression, and skin-soft tissue infection), all but age remained in the final model. Although the risk model showed good discrimination (AUC-ROC, 0.77; 95% confidence interval, 0.72-0.82), sensitivity was 67% (specificity 76.5%). Once model was developed with the derivation population (11998 patients, 2/3 of 2010 population), we perform a validation with the remaining 4952 (1/3). For this validation population, AUC-ROC was 0.72 (95% confidence interval, 0.65-0.79) and a p=0.539 on the Hosmer-Lemeshow goodness of fit test. In the light of the findings, we tried a new model in the event that a patient is admitted from other ICUs, so we included variables used for the first model and others that can be present either on admission or during ICU stay, (so-called "complete model") as urinary catheter, parenteral nutrition, extra-renal dialysis, non-invasive ventilation, tracheostomy, arterial catheter, enteral nutrition,

Table 1 - Variables associated with C /I by MRSA in ICU, independent on the time of detection (on admission or once in ICU).

		Multivariate		
Risk factor		*RR*	*CI 95%*	*p*
Gender	Male	Reference		
	Female	0.75	(0.65-0.87)	<0.001
Age	<52	Reference		
	65-74	1.25	(1.02-1.52)	0.028
	=>75	1.25	(1.03-1.53)	0.027
Type of patient	Coronary	Reference		
	Medical	2.00	(1.46-2.75)	<0.001
	Trauma	1.77	(1.22-2.55)	0.002
APACHE	<8	Reference		
	8-12	1.52	(1.10-2.08)	0.01
	13-18	1.60	(1.20-2.15)	0.002
	>18	2.07	(1.54-2.77)	<0.001
Origin	Hospital ward	Reference		
	Community	0.72	(0.62-0.83)	<0.001
	Long-term care facility	2.90	(1.85-4.55)	<0.001
Immunodeficiency	No			
	Yes	0.52	(0.31-0.88)	0.014
Superficial post-surgical skin infection	No			
	Yes	1.62	(1.12-2.34)	0.016
Skin-soft tissue infection	No			
	Yes	1.57	(1.09-2.27)	0.015

APACHE: Acute Physiology and Chronic Health Evaluation II; RR: rate ratio; CI: confidence interval.

Table 2 - Predictive model for MRSA-C/Ion ICU admission with easy-to-know variables (Simple Model).

		OR	*CI 95%*	*p*
Male Gender		1,66	(1,04-2,64)	0,03
Type of patient	Coronary	Reference		
	Medical	Not significant		
	Trauma	14,10	(1,90-103,70)	0.01
	Surgical	Not significant		
Urgent surgery		2,30	(1,75-4,99)	<0,001
Origin	Community	Reference		
	Other ICU	2,33	(1,42-3,83)	<0,001
	Hospital ward	3,86	(1,56-9,59)	0,004
	Long-term care facility	16,77	(6,92-40,59)	<0,001
Immuno-suppression		1,87	(1,05-3,30)	0.03
Skin-soft tissue infection		4,60	(1,06-20,19)	0.04

CI: Confidence interval; OR: odds ratio; CI: confidence interval.

nasogastric tube, and severity by APACHE score. For this complete model, AUC only improved to 0.82 (95% confidence interval, 0.77-0.86), and sensitivity was 63.64% and specificity 78.48%), in comparison with AUC-ROC=0.77 of the "simple model".

DISCUSSION

After studying the whole population of the study, regardless of when they acquired the pathogen (2006-2010), our findings were similar to those published in literature and we conclude that our sample is representative of standard critical care population. Most of the risk factors identified in the multivariable analysis for MRSA-C/I in ICU have been described in previous studies in general hospitalized non-critical patients, but to a lesser extent in ICU patients (Table 1). As regards origin, caution should be taken with cases admitted to ICU from a long-term care facility, where more complex patients, with invasive devices, antibiotic treatment or skin ulcers, are discharged increasingly earlier from acute hospitals. We did not find any increase in the risk of MRSA-C/I in patients admitted from other ICUs, perhaps because all patients usually share the same microbial ecology if both ICUs are in the same hospital and, if not, transfers to reference centers are made usually the first hours/days after admission. Patients under immunosuppressant therapy (acute high dosage or chronic steroids, chemo/radiotherapy or advanced active solid or hematologic malignancy) were more likely to be MRSA-C/I on admission (Table 2), but not during ICU stay (as happens with immunodeficiency - a variable that included neutropenia and congenital or acquired immunodeficiency - that emerged as protective factor during ICU stay). This shows that if an immunosuppressed patient is admitted in ICU, it may be more likely to be C/I by MRSA but, if there is no MRSA on admission, during ICU stay the patient will be protected by isolation precautions from the beginning, as well as patients with immunodeficiency. Finally, although in our study there is an increase in the risk of being MRSA-C/I if a patient is C/I by other MDRO (also described in critical patients), we did not include those variables in the multivariate analysis, as they can be explained by cross contamination and by the fact that similar risk factors for nosocomial colonisation and infection have been described for various MDRO [24, 25].

Once we were sure that our sample had enough quality in statistical terms to extrapolate our results, we focus our analysis strictly on ICU admission. As for the prediction of the presence of MRSA, to our knowledge this is the first work to develop a predictive model for MRSA-C/I specifically for the time of admission in ICU in which all critical patients are represented, and based exclusively on demographic/clinical risk factors, easy to collect by clinicians. The resulting model

("Simple model" - Table 2), has a good overall prediction index, but with sensitivity not high enough to base initial empirical antibiotic treatment on the model or to help to decide which patient should be isolated to prevent cross transmission of MRSA. The addition to the model of more risk factors that can be present during ICU stay (on the assumption that a patient is admitted referred from another ICU - "Complete model") does not improve its predictive capability.

Several attempts have been made to develop simple and cost effective prediction rules to identify patients colonized or infected by MRSA. In those studies, critical patients are either integrated into the overall hospitalized population or excluded from the studies. Only two were focused on ICU patients [26, 27]. Both excluded pre-existing MRSA on admission, and none of the models described can be used strictly on ICU admission. Minhas et al. studied, with a retrospective-univariate analysis only, MRSA acquisition once a MRSA-negative patient is admitted into a single-center specific Neurocritical Care Unit for more than 48 hours [27]. In their prospective single-center study, Yamakawa et al. included for their multivariate model, variables obtained during the first 24 h of stay, once the patient had been admitted in ICU [26]. They found that performing preemptive infection control measures on intubated patients in the first 24 hours or those with open wounds, they covered 96.7% of the patients infected with MRSA, and the number of those with these two factors would be limited to just 57.4% of all admitted. But the purpose of the study was to identify the risk factors for healthcare-associated MRSA infection (not colonisation) in the patients who did not harbor MRSA at the time of ICU admission. They separately investigated predictors of infection for patients with MRSA on ICU admission, but due to the small sample (n=19), no prediction was possible.

There are several reasons that can contribute to the low sensitivity of our model. Limiting the risk factors studied only to those easy-to-know on admission increases the usefulness of the prediction tool, but it also means that we have to exclude some well-known factors associated with MRSA, like previous antibiotic therapy or previous colonisation. There is also the possibility of an underestimation of MRSA rates, as microbiological surveillance policy on ICU admission is not uniform. Although most ICUs in Spain systematically obtains surveillance cultures on all patients admitted in the unit, or at least on those suspected of being C/I by a MDRO, our MRSA incidence may be equivocal as the positivity rate expected could be higher in units that perform universal nasal swab due to screening protocols compared with others that do not perform screening at all. Traditionally, our MRSA rates are very low in comparison with other countries like USA, in which a prevalence on admission of 8%, and incidence during ICU stay of 5% has been described [28]. In addition, to make prediction tools easier to extrapolate, our study includes more than 11000 of all types of critical patients, not focused on certain ICU populations or diseases, and including specific and non-specific units (medical, traumatological, neurocritical, burns ICU …) throughout the country, not taking into account local particularities, that can impact on the development and generalization of predictive rules [21, 23].

In addition, our study has certain limitations that should be acknowledged. Among them is that ENVIN-HELICS registry is not designed specifically for the purpose of our analysis, so we used the database as a kind of multipurpose cohort, but external audits confirm the reliability of the data even if we search for risk factors not related to invasive devices. As regards the Poisson regression of the risk factors, we could not discriminate until year 2010, between known and unknown MRSA carriers on admission and included previously MRSA carriers in the multivariate analysis. This may not be considered as a limitation itself, as many ICUs worldwide have not adopted universal isolation and surveillance. The methodology used to detect multi-drug resistant pathogens was also not uniform across all ICUs. We did not distinguish between healthcare associated-MRSA (HA-MRSA) and CA-MRSA, as the incidence in Spain of the latter is minimal (but its impact could not be demonstrated, as molecular typing of isolates was not performed).

In any case, a rapid high sensitive diagnostic tool is still needed, that allows clinicians to reliably suspect if their patient is C/I due to MRSA on admission. As rapid laboratory tests improve, there is a trend to rely only on them and abandon the study of risk factors. Among those tests, real-time PCR is the most used as it is getting better, easier,

and cost-effective, although it also has limitations [21, 29-31]. Additionally, although result of the test is available in a couple of hours, the reality of the human and technical hospital resources shows a mean of 13-21 hours between detection and communication of the results to clinicians, sometimes close to the 24 hours from which real-time-PCR is considered not to be cost-effective [32-34]. Those reasons emphasize the need of continuing the study of MRSA risk factors to use either alone or in combination with rapid laboratory tests.

CONCLUSIONS

Independent risk factors for MRSA colonisation/infection during ICU stay and on ICU admission are described. Although the AUC-ROC obtained in the different prediction models seems to be promising, the low sensitivity that we found would result in missing an unacceptably high proportion of MRSA-C/I in the ICU setting. In our opinion, and with the evidence available, risk factors should not be used solely to predict the presence of the pathogen. Clinical-demographic risk factors for colonisation/infection related to MRSA should not be used to accurately identify patients who would benefit from empirical anti-MRSA treatment or from specific preventive measure. The combination of a risk prediction model to estimate the pretest probability for MRSA on admission, calibrated with the local conditions of the different ICU, along with a rapid laboratory test could be the way to proceed in future studies for MRSA prediction [35]. For those studies, the independent risk factors described should be taken into consideration.

Conflicts of Interest and Source of Funding
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Statement about previous presentation of the data
Some of the information of the article was used to create an abstract for a poster accepted in the 35th International Symposium of Intensive Care and Emergency Medicine (Brussels, March 2015).

Authors contributions
F. Callejo-Torre analyzed the data, and wrote the manuscript, JM. Eiros Bouza and MJ. Coma Del Corral participated in the design and revised the manuscript, P. Olaechea Astigarraga as ENVIN-HELICS Study Group Coordinator developed ENVIN registry database and revised the manuscript, M. Palomar Martínez, F. Alvarez-Lerma and MJ. López-Pueyo as ENVIN-HELICS Study Group Coordinator developed ENVIN registry database. All authors have seen and approved the final version. Statistical analysis was performed by Prof. Dr. Cristina Fernández Pérez, Head of the Methodology and Clinical Epidemiology Department of the Preventive Medicine Unit of the Hospital Clínico San Carlos of Madrid. The Statistics Departments of the Research Unit of the Hospital Universitario de Burgos and Valladolid University also collaborated.

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