Journal of Global Antimicrobial Resistance 2 (2014) 27–33

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* colonisation in a large metropolitan area in Greece: An epidemiological study using two case definitions

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ARTICLE INFO

Article history:
Received 15 May 2013
Received in revised form 28 August 2013
Accepted 1 October 2013

Keywords:
MRSA
Community acquired
Hospital acquired
Co-morbidities
Centers for Disease Control and Prevention

ABSTRACT

The aim of this study was to evaluate the epidemiology and characteristics and to identify modifiable risk factors for community-associated (CA) MRSA colonisation in a region with high prevalence. A large patient population ($n = 2280$) from two tertiary care centres in Athens (Greece) was evaluated. Demographics and potential risk factors for CA-MRSA colonisation were recorded prospectively. Presence of the Panton-Valentine Leukocidin (PVL) toxin and *mecA* gene was determined in all MRSA isolates. Two definitions for CA-MRSA were applied. Univariate and multivariate analyses to identify predictors of previously unknown CA-MRSA colonisation were performed. In total, 120 (5.3%) MRSA carriers were identified; in 67 the isolates were classified as CA-MRSA using criteria based on the CDC definition, compared with 35 based on a definition including PVL toxin positivity. Factors significantly associated with previously unknown CA-MRSA carriage (CDC definition) included being a child or adolescent (OR = 3.6, 95% CI 1.5–8.6), belonging to the family of an index case (OR = 2.4, 95% CI 1.2–4.8), and presence of any co-morbidity (OR = 1.7, 95% CI 1.04–2.8) or chronic skin disease (OR = 3.6, 95% CI = 2.2–6.1). In multivariate analysis, presence of any co-morbidity was the only significant predictor (OR = 4.9, 95% CI 1.07–22.5; $P = 0.04$). No easily modifiable risk factor for previously unknown CA-MRSA colonisation was identified. The CDC-based epidemiological definition for CA-MRSA appears to be more sensitive in detection of CA-MRSA colonisation than a purely molecular definition based on presence of the PVL gene.

1. Introduction

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), both hospital-acquired and community-acquired, remain a worldwide problem, adding to the overall burden of infectious diseases. The epidemiology of MRSA is evolving. Initially, MRSA strains were classified according to the origin of the patient and the probable source of acquisition of the pathogen as community-acquired MRSA (CA-MRSA) or hospital-associated MRSA (HA-MRSA). In contrast to HA-MRSA, CA-MRSA was often identified as a cause of infection in otherwise healthy young people and had a different antimicrobial susceptibility profile than its nosocomial counterpart. Recently, experts have challenged these conventional definitions and have proposed new classifications [1].

Risk factors of CA-MRSA acquisition and colonisation are still incompletely understood. As an example, prior antibiotic use has not been consistently identified as a risk factor for CA-MRSA [2–4], although the opposite is true for hospital-acquired strains [5,6]. Furthermore, risk factors may not be uniform in different settings; for instance, it still remains unclear why clusters of CA-MRSA infection among high-risk groups such as injection drug users, military recruits and sports teams are still uncommon in Europe compared with the USA and Canada [7,8].

Few formal studies evaluating risk factors for CA-MRSA colonisation and infection have been performed in Greece [9]. In most of these studies, clinical cases with an infection were studied and CA-MRSA was associated with skin and soft-tissue infections

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2213-7165/$ – see front matter
http://dx.doi.org/10.1016/j.jgar.2013.10.001

in children, belonging to the well described sequence type 80 (ST80) clone spreading throughout Europe [8–11].

The aim of the current study was to evaluate the current epidemiology and characteristics of CA-MRSA colonisation in Athens (Greece) and to attempt to identify modifiable risk factors for colonisation among previously unknown MRSA carriers.

2. Methods

The current study was designed as a retrospective case–control study that tested the following specific hypotheses: (a) previous antibiotic exposure is not associated with CA-MRSA colonisation in Athens; (b) CA-MRSA colonisation is related to specific demographic features; (c) cluster effects (e.g. family transmission) are important; and (d) epidemiological and molecular CA-MRSA case definitions differ in their sensitivity to identify previously unknown CA-MRSA carriers.

This population-based, retrospective case–control study was based on two prospectively collected data sets of patients visiting two major tertiary care hospitals covering a population of ca. 2 million people in the metropolitan area of Athens. All patients identified as colonised or infected with MRSA strains between January 2009 and October 2010 were included in the study. Laikon General Hospital (LGH) participated in the MOSAR WP4 trial[12], an EU-funded, multicentre, interventional cohort study on MRSA control (clinicaltrials.gov NCT00685867), during which active MRSA screening (nasal and inguinal swabs) was performed in all patients admitted to surgical wards. The second data set was used from Attikon General Hospital (AGH) and involved consecutive outpatients visiting the Infectious Diseases Clinic of AGH who were all prospectively screened for MRSA (nasal, inguinal and axillary swabs). Isolates were cultured and subsequent molecular detection of *mecA* and Panton–Valentine leukocidin (PVL) genes from colonies was performed.

For the purpose of this case–control study (study inclusion criterion) and for both data sets (AGH and LGH), two definitions for CA-MRSA were used that have been previously used in studies of clinical infections with this pathogen. More specifically, CA-MRSA was initially defined as any MRSA strain that: (a) exhibited antimicrobial resistance to oxacillin and cefoxitin; (b) harboured the PVL toxin and *mecA* gene; and (c) was isolated from a patient without hospitalisation within the last 12 months. Any patient not colonised or infected with MRSA independent of admission status during the same study period was used as a control. For each CA-MRSA case eligible for the study that belonged to the MOSAR data set, up to four randomly selected patients admitted during the same study period were chosen as controls. For the AGH data set, all negative cases were used as controls.

In a second analysis, the accuracy of a purely epidemiological case definition was determined using the US Centers for Disease Control and Prevention (CDC) criterion for CA-MRSA that is independent of PVL status [13]. The CDC defines CA-MRSA as MRSA that has been isolated from patients who have no history of (a) positive culture for MRSA from any body site obtained >48 h after admission to a hospital (if hospitalised), (b) prior MRSA infection or colonisation, (c) hospitalisation, surgery, residency in a long-term care facility, haemodialysis or peritoneal dialysis within the past year or (d) current indwelling percutaneous devices or catheters [13].

Patients with a history of HA-MRSA colonisation or infection (i.e. onset 48 h after hospital admission, or healthcare contact within the last 12 months) and infections due to the prevailing HA-MRSA strains in the different settings were excluded from the study.

Information regarding patient demographics, clinical presentation and exposure to possible risk factors during the last 12 months was collected through standardised questionnaires that included data on several possible risk factors for CA-MRSA acquisition such as outpatient visits, underlying medical condition (e.g. diabetes mellitus), previous antibiotic use within 1 year, dermatological condition, household contact with MRSA-infected persons, occupation as healthcare worker or close contact with a healthcare worker (family member), day-care attendance and other potential explanatory variables (e.g. team sport activities, homosexuality, drug abuse, animal contact). For all study participants with an MRSA isolate, the antibiotic susceptibility profile, presence of the *mecA* gene and presence of the PVL gene of the isolate were recorded. A paper-based data collection system was used for the study. Special attention was paid to preserve confidentiality during data collection and data transfer. The study was approved by the Institutional Review Boards of both institutions.

Crude (univariate) analyses comparing correlates of CA-MRSA versus no carriage were conducted initially. For contrasts of dimensional variables, Student's *t*-test or the Wilcoxon rank-sum test was used. A two-tailed χ^2 test or Fisher's exact test, when indicated, was used to compare proportions. Continuous variables were converted to categorical variables if they did not fulfil criteria of linearity. Then, multivariate conditional logistic regression models for matched data sets were used to estimate odds ratios (ORs) and to determine risk factors for previously unknown CA-MRSA carriage and infection. Models were built including all variables associated with the outcome at a significance level of $P < 0.2$. Any variable for which the χ^2 statistic of the likelihood ratio test indicated no statistical significance ($P > 0.05$), and no substantial confounding of OR estimates for the other variables was observed, was subsequently eliminated from the model. Possible effect modification of different variables was analysed by fitting interaction terms between variables; resulting models were compared by likelihood ratio tests. Results are presented as crude (unadjusted) and multivariate (adjusted) ORs and their 95% confidence intervals (CIs).

3. Results

In total, 2280 patients were included in the study: (a) the first population comprised subjects from the MOSAR cohort from LGH ($n = 924$) who were prospectively screened for MRSA colonisation during admission to surgical wards; and (b) the second population consisted of participants from a prospective outpatient MRSA screening protocol performed at AGH ($n = 1356$). Nine patients with a previous history of HA-MRSA colonisation or infection were excluded from the analysis. Only one patient had an active CA-MRSA infection, whereas all others were classified as colonised. In total, 120 MRSA-colonised individuals were newly identified; 35 were classified as CA-MRSA according to the primary study definition and 67 as CA-MRSA according to the CDC criteria, since a significant percentage of CA-MRSA isolates in the study were PVL negative [28 (44%) of 63 isolates with evaluable results]. The majority of the CA-MRSA-colonised individuals came from the AGH outpatient population [48 (72%) of the 67 colonised individuals]. Among 62 children and adolescents, 6 were colonised with CA-MRSA.

Features of all MRSA-colonised individuals (including HA-MRSA and CA-MRSA) in univariate comparison with the control population are presented in Table 1. Factors significantly associated with previously unknown MRSA carriage included (Table 1): (a) the presence of co-morbidities (for any co-morbidity, OR = 2.7, 95% CI 1.8–3.9; $P < 0.001$); (b) history of hospitalisation during the previous year (OR = 1.8, 95% CI 1.2–2.6; $P = 0.005$) or being a resident of a nursing home/rehabilitation centre (OR = 18.8, 95% CI 5.4–65.8; $P < 0.001$); (c) use of antimicrobials during the last 6 months (OR = 1.5, 95% CI 1.02–2.2; $P = 0.04$); (d)