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Brief Communication

Incidence and treatment of methicillin-resistant S. *aureus* infection in cystic fibrosis patients: a cohort study

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ABSTRACT

In Brazil the knowledge about methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis patients is scarce. This study aimed to determine the incidence of respiratory tract colonization and the identification rates after a standardized treatment. A retrospective cohort was performed highlighting the history of respiratory colonizations between January 2008 and June 2015. Patients under the age of 21 years with cystic fibrosis confirmed by sweat test or genetic study receiving care at the outpatient clinics of a Teaching Hospital were included. The treatment consisted of trimethoprim/sulfamethoxazole, rifampicin, nasal mupirocin and chlorhexidine 2%. The mean follow-up period was of 22.2 months and those with ≥3 negative cultures were considered free of methicillin-resistant *Staphylococcus aureus*. Forty-two patients were included. Methicillin-resistant *Staphylococcus aureus* was identified in six patients. Most patients had methicillin-sensitive *S. aureus* isolation prior to methicillin-resistant *Staphylococcus aureus*. Five children used the standardized treatment, none presented side effects. Only one child had a new isolation of methicillin-resistant *Staphylococcus aureus* during follow-up (after 20 months). The incidence of methicillin-resistant *Staphylococcus aureus* infection was high and occurred in young patients. The therapeutic regimen was effective, safe and being a good option to treat methicillin-resistant *Staphylococcus aureus* infection.

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Cystic fibrosis (CF) clinical manifestations are highly variable and respiratory tract infections (RTI) are responsible for high morbidity and mortality rates. Identifying and better understanding the respiratory tract pathogens in those patients is therefore of utmost importance.[1]

Staphylococcus aureus is one of the first and most frequent pathogens to be isolated from the respiratory tract in CF patients.[2] This microorganism is a Gram-positive coccus with a typically aerobic metabolism that can also perform as a facultative anaerobic and is capable of producing biofilm.[2]

In the last decades the increased life expectancy of CF patients can be related to advances in the treatment of chronic pulmonary infections and also to patient follow-up by multidisciplinary healthcare teams.[1] The emergence of multi-resistant microorganisms is mainly a result of multiple antibiotic cycles in the treatment of RTI[1] and to long-lasting hospitalizations.[3]

The isolation of methicillin-resistant *S. aureus* (MRSA) was first observed in 1961.[2] Resistance is acquired through the mecA gene located on the *Staphylococcal cassette chromosome mec* complex (SCC*mec*).[4] Based on its structural composition, 11 different types (I-XI) and various subtypes of SCC*mec* have been recognized in MRSA so far.[3,4] Initially, MRSA infections were only described in the hospital environment. However, in the 90s MRSA began to be observed also in the community.[2]

The prevalence of MRSA colonization in CF patients has been increasing in the USA for the last 15 years,[2,3,5,6] being variable in diverse geographic regions, ranging from 2.7% in the United Kingdom to 30% in the United States.[2,3,7,8] There are doubts regarding the natural course and pathogenic importance of the infection caused by this microorganism, although it is possibly associated with a more rapid decrease in lung function and higher morbidity and mortality.[9,10] The role of MRSA eradication treatment in order to prevent chronic infection is also unclear[3] and there is no consensus about the ideal therapeutic regimen and various regimens are currently in use.[2,3,11]

In Brazil the knowledge about MRSA colonization in CF patients is scarce. A study carried out in 2006 in a reference center in Bahia identified that the frequency of MRSA colonization was 6%[12] and Simon et al.[13] detected a frequency of 18.8% in CF patients at a center in Porto Alegre. Data from the Brazilian Cystic Fibrosis Registry (BCFR) show a frequency of MRSA isolation varying from 7.8% to 9.3% between 2009 and 2013.[14]

This study aimed to determine the incidence of respiratory tract colonization by MRSA and to assess the persistence rates of the microorganism after administering a standardized treatment in CF pediatric patients followed at the Multidisciplinary Cystic Fibrosis Clinic at the Prof. Edgard Santos Teaching Hospital, Salvador, Brazil. This clinic provides treatment for children and adolescents (0–20 years old) mostly from low income families and with high level of miscegenation.

A retrospective cohort study was conducted searching for history of respiratory colonization among CF children and adolescents under 21 years of age followed at the Multidisciplinary Cystic Fibrosis Clinic at the Prof. Edgard Santos Teaching Hospital in the period of January 2008 and June 2015. The patients included in the study had a CF diagnosis confirmed by elevated sweat chloride tests on two different occasions.

Data used in this study were retrieved from patients' medical charts and the following variables were collected: sex; ethnicity; current age, age at the diagnosis and age at the first isolation of methicillin-sensitive *S. aureus* (MSSA) and MRSA; number of MRSA-positive samples for each patient; previous MSSA identification; *Pseudomonas aeruginosa* prior to and/or after the MRSA isolation; genotype; use of standardized treatment.

Patients' follow-up visits at the Multidisciplinary Cystic Fibrosis Clinic usually were scheduled every three months and collection of respiratory secretions by the physiotherapist is done at every visit. Samples were preferably obtained via expectorated sputum or by oropharyngeal swab when the former way was not possible and the material was immediately sent to the microbiology lab for culture. Upon arrival, samples were processed in blood agar, chocolate agar, MacConkey agar and selective medium for *Burkholderia cepacia* complex. Plates with creamy white hemolytic colonies, suggestive of *S. aureus*, were Gram stained and the phenotypic coagulase test was performed using Staphytest – PROBAC®. Gram-positive coagulase-positive samples were then submitted to an antimicrobial susceptibility test for the detection of MRSA using a cefoxitin 30 g disk in Mueller–Hinton medium. Cefoxitin-resistant isolates were considered MRSA according to the Clinical and Laboratory Standards Institute (CLSI).[15] The standard American Type Culture Collection (ATCC) *S. aureus* was used as a control for the quality of the medium and disks used.

All patients with MRSA isolation between January 2013 and August 2014 received a standardized treatment consisting of an oral association of trimethoprim/sulfamethoxazole plus rifampicin for 14 days, besides nasal mupirocin and corporal hygiene of the patient and family members with chlorhexidine 2%, both for one week. After treatment, patients were followed-up until June 2015 and those with at least three negative cultures during this period were considered free of MRSA.

Descriptive analysis was performed using Epidata software and the following descriptive statistics were calculated: median, mean, standard deviation, amplitude, simple and relative frequencies. The study was approved by the Internal Review Board of Prof. Edgard Santos Teaching Hospital under approval number 121/2011. Informed consent statements were signed by one of the parents, for patients under 18 years old, and, for the others, by the own patient.

Overall, 42 patients were included in the study with a mean age of 9.9 years (SD = 5.4) ranging from 1 to 20.8 years. From those, 22 (52.4%) patients were male. Eight patients followed at the cystic fibrosis Clinic were excluded: three had suppurative lung disease and chronic respiratory tract colonization by mucoid *P. aeruginosa* but normal sweat tests, and three had borderline sweat tests. All patients were non-white. The allelic frequency for the Phe508del mutation was 25%. During the study period, MRSA was identified in six patients (14.3%) and their clinical data are displayed on Table 1. Two children had more than one isolation of this microorganism (four and eight, respectively). The sensitivity profiles of this microorganism showed susceptibility to trimethoprim/sulfamethoxazole and vancomycin, among other tested antibiotics.

In the six patients in whom MRSA was isolated, the median age at CF diagnosis was 8 months, varying from three to