Nasal Carriage of Multi-Drug Resistant Panton-Valentine Leucocidin-Positive Methicillin-Resistant *Staphylococcus aureus* in Children in Tripoli-Libya

Omaima H. Al-haddad, Abdulaziz Zorgani, and Khalifa Sifaw Ghenghesh*

Faculty of Pharmacy and Faculty of Medicine, University of Tripoli, Tripoli, Libya

Abstract. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonized children are at an increased risk of developing infections than methicillin-sensitive *S. aureus* colonized children. Nasal specimens from inpatient children, mothers of inpatient children, healthcare workers, and outpatient children at Tripoli Children Hospital (TCH) were examined for MRSA by chromogenic MRSA ID medium. Susceptibility of MRSA isolates to antibiotics was determined by the disc diffusion method. The nasal carriage rate of MRSA among inpatient children (8.3%, 24 of 289), their mothers (11%, 22 of 200), and healthcare workers (12.4%, 22 of 178) was significantly higher than among outpatient children (2.2%, 2 of 91) ($P < 0.05$, $P < 0.02$, and $P < 0.006$, respectively). Of the examined MRSA isolates ($N = 35$) 10 (28.6%) were positive for Panton-Valentine leucocidin genes by polymerase chain reaction. Multidrug resistance was found in 24.3% (17 of 70) of MRSA isolates. Nasal carriage of multidrug-resistant Panton-Valentine leucocidin-positive MRSA is not uncommon among inpatient children and their mothers in Tripoli.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of healthcare-associated (HA) and community-associated (CA) infections worldwide.^{1,2} The MRSA is characterized by its resistance to β -lactam antibiotics and acquiring resistance to several groups of other drugs that result in longer hospital stays and increased cost of treatment.³

The CA-MRSA affect healthy children without the risk factors usually linked with HA-MRSA infections.⁴ Compared with HA-MRSA, CA-MRSA are often less resistant to several groups of non-lactam antimicrobial agents and frequently carry the genes *lukS-PV* and *lukF-PV* coding for the cytotoxin Panton-Valentine leucocidin (PVL).

The MRSA colonized patients are at increased risk of developing infections than methicillin-sensitive *S. aureus* (MSSA) colonized patients.⁵ There is little information regarding the nasal carriage of multidrug-resistant (MDR) PVL-positive MRSA in children in countries of North Africa (including Libya) and the Middle East. The objective of this investigation was to determine the prevalence of nasal colonization with MDR PVL-positive MRSA in children in Tripoli, Libya.

METHODS

This study was carried out in Tripoli Children Hospital (TCH), Tripoli during the period June 2009 to September 2010. The TCH has 335 beds and receives nearly 6,000 patients per year. Included in the study were 758 nasal specimens collected within 48 hours from admission from inpatient children ($N = 289$) and mothers of inpatient children ($N = 200$) in the Departments of General Pediatrics and Nephrology, and Pediatric Intensive Care Unit (PICU). In addition, nasal specimens were obtained from healthcare workers (HCWs; physicians [$N = 87$], nurses [$N = 82$], and cleaners [$N = 9$]) and outpatient children ($N = 91$) at the outpatient clinic. Furthermore, nasal specimens were collected at discharge from 77 evaluable inpa-

tient children that were MRSA-negative on admission. The latter group hospitalization period range was 4–15 days (mean = 4.7 days). Patient age, gender, admitting specialty, and associated health risk factors were obtained for each patient.

In this investigation, nasal specimens were collected under approved ethical standards and the study was reviewed and approved by the Faculty of Pharmacy and the Department of Post Graduate Studies at Tripoli University. Informed consent was granted by the children's parents and the HCWs (physicians, nurses, and cleaners) before specimen's collection.

Specimens were collected from the anterior nares with premoistened, sterile cotton-tipped swabs and processed within 3 hours of collection. Swabs were inoculated on to mannitol salt agar (MSA) and nutrient agar (NA) and incubated at 37°C overnight. Colonies from MSA and NA were tested for production of catalase and coagulase (by both slide and tube tests). Colonies identified as *S. aureus* were tested for production of green colonies on chromogenic MRSA ID medium (bioMérieux, Marcy L'Etoile, France) according to the manufacturer's instructions. Randomly selected 35 MRSA isolates identified by chromogenic medium were further tested for *mecA* and PVL-encoding genes (*lukS-PV* and *lukF-PV*) by polymerase chain reaction (PCR) techniques as previously described.^{6,7} Molecular typing of MRSA isolates ($N = 12$) obtained from four inpatient children, their mothers, and from four HCWs in ICU was performed by pulsed field gel electrophoresis (PFGE) as previously reported.⁸ The MRSA isolates were tested for resistance to antimicrobials by the disc diffusion method recommended by the Clinical Laboratory Standards Institute.⁹ The following antimicrobial discs were used: ciprofloxacin (5 μ g), clindamycin (2 μ g), pristinamycin (15 μ g), erythromycin (15 μ g), gentamicin (10 μ g), fusidic acid (10 μ g), mupirocin (20 μ g), trimethoprim-sulfamethoxazole (25 μ g), and vancomycin (30 μ g) (Oxoid, Basingstoke, Hampshire, UK).

Cases were classified according to Centers for Disease Control and Prevention (CDC) criteria as previously reported.^{10,11} Prior MRSA infection was not included in the risk factors sought because of a lack of records. Therefore, healthcare-associated community-onset (HACO) MRSA cases were identified as those for which cultures were collected from outpatients or < 48 hours after hospital admission from patients with the following risk factors: ICU admission, surgery, residence in chronic care facility, or exposure to a dialysis

*Address correspondence to Khalifa Sifaw Ghenghesh, Faculty of Medicine, University of Tripoli, Tripoli, Libya. E-mail: ghenghesh_micro@yahoo.com

unit. The CA-MRSA cases were those for which cultures were from outpatients or < 48 hours after hospital admission from patients without risk factors. No hospital-onset MRSA cases were included in the study.

For statistical analysis, Epi Info 2000 software (CDC, Atlanta, GA) was used. *P* values were calculated using a χ^2 test. *P* < 0.05 was considered to be statistically significant.

RESULTS

Of the 758 individuals examined *S. aureus* (both MSSA and MRSA) was detected in 27.4% and MRSA in 9.2%. The nasal carriage rate of MRSA among inpatient children (8.3%, 24 of 289), their mothers (11%, 22 of 200), and HCWs (12.4%, 22 of 178) was significantly higher than among outpatient children (2.2%, 2 of 91) (odds ratio [OR]: 4.03, *P* < 0.05, OR: 5.50, *P* < 0.02, and OR: 6.28, *P* < 0.006, respectively). In addition, the carriage rate of MRSA among cleaners (33.3%, 3 of 9) was significantly higher than among children (6.8%, 26 of 380), regardless of whether they are inpatients or outpatients (OR: 6.81, *P* < 0.003). No significant differences were observed in the nasal carriage rate of *S. aureus* among groups examined. Table 1 shows the nasal carriage of *S. aureus* and MRSA among children (inpatients and outpatients), mothers of inpatient children, and HCWs in Tripoli.

Among inpatient children *S. aureus* and MRSA were detected in 21.6% (25 of 116) and 6.9% (8 of 116) of age group *P* < 1 year, in 28.9% (33 of 114) and 8.8% (10 of 114) of age group 1–5 years, and in 30.5% (18 of 59) and 10.2% (6 of 59) of age group *P* > 5–15 years, respectively. The differences in the detection of *S. aureus* and MRSA among inpatients of different age groups were not statistically significant. In addition, *S. aureus* and MRSA were detected in 26.3% (44 of 167) and 7.8% (13 of 167), of inpatients in the General Pediatrics Department, in 27.5% (22 of 80) and 11.8% (9 of 80) of inpatients in the ICU, and in 25% (10 of 40) and in 4.8% (2 of 40) of inpatients in the Nephrology Department. The differences in the detection of *S. aureus* and MRSA among inpatients in different departments were not statistically significant. Furthermore, none of the 77 MRSA-negative inpatient

children on admission were positive for the organism when examined at discharge.

Of the MRSA-positive inpatients 70.8% (17 of 24) were with one or more risk factors (i.e., HACO-MRSA cases) and the remainder inpatients (29.2%, 7 of 24) were without a risk factor (i.e., CA-MRSA cases). The two MRSA-positive outpatient children were both without a risk factor.

Of the 24 MRSA-positive inpatients, 13 (54.2%) used antibiotics in the past 6 months before admission and information from only six of them was available regarding the type of antibiotic used; three used amoxicillin and cefotaxime, two amoxicillin-clavulanic acid combination and cefotaxime, and one used cefixime.

Of the total MRSA isolated in this work (*N* = 70), resistance to ciprofloxacin was observed in 31.4%, to gentamicin in 34.3%, and to fusidic acid in 48.6%. All (100%) MRSA isolates were susceptible to mupirocin, trimethoprim-sulfamethoxazole, and vancomycin. Multidrug resistance (resistance to three or more drugs) to non-beta-lactams was found in more than 25% of total MRSA isolates. No significant differences were observed in the resistance rates to ciprofloxacin, clindamycin, erythromycin, gentamicin, and fusidic among MRSA isolated from children, mothers, and HCWs. Multidrug resistance (resistance to three or more antimicrobials) to non-β-lactams was observed among 24.3% (17 of 70) of total MRSA isolates. Although MDR was observed at a higher rate among MRSA from pediatrics (30.7%, 8 of 26) than among MRSA from mothers (18.2, 4 of 22) and HCWs (22.7, 5 of 22), the differences were not statistically significant (*P* > 0.05). Supplemental Table 1 shows antibiotic resistance profiles of isolated MRSA from children, mothers, and HCWs.

Of the examined MRSA isolates 35 (100%) were positive for the *mecA* gene and 10 (28.6%) were positive for PVL genes. Only 18 MRSA from inpatient children (12 HACO-MRSA cases and 6 CA-MRSA cases) were tested for PVL genes. The genes were detected in 41.7% (5 of 12) of HACO-MRSA cases and in 16.7% (1 of 6) of CA-MRSA cases. Five PFGE types (A–E) were found among 12 MRSA examined according to Tenover and others criteria,¹² with predominance of type A (58.3%, 7 of 12). The MRSA was cultured from four mother–child pairs, three pairs had the same PFGE type (two type A and one type B) and antibiotic resistance profile. Only one inpatient child and his mother were positive for PVL genes. Supplemental Table 2 shows PFGE types, antibiotic resistance profiles, and presence of PVL genes among MRSA isolates from four inpatient children and their mothers and four HCWs.

DISCUSSION

Methicillin-resistant *S. aureus* carriage is a risk factor for succeeding MRSA infection in children.¹³ Reported nasal carriage rates of MRSA from children vary from one country to another and within the same country depending on populations studied and associated risk factors with lower nasal carriage rates being reported from healthy children. A Brazilian study reported a nasal carriage rate of 31.1% (371 of 1,192) for *S. aureus* and 1.2% (14 of 1,192) for MRSA among healthy children 5 years of age or less attending 62 day care centers.¹⁴ We found an overall nasal carriage rate of 6.8% for MRSA among Libyan children, however, a significantly higher carriage rate observed in inpatient compared with outpatient

TABLE 1

Nasal carriage of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) among children and their mothers and healthcare workers (HCWs) in Tripoli

Groups sampled	No. samples	No. (%) <i>S. aureus</i> *	No. (%) MRSA†	No. (%) MRSA‡
Children	380	96 (25.3)	26 (6.8)	26 (27)
Inpatients	289	76 (26.3)	24 (8.3)§	24 (31.6)
Outpatients	91	20 (23)	2 (2.2)	2 (10)
Mothers¶	200	67 (33.5)	22 (11)	22 (32.8)
HCWs	178	45 (25.3)	22 (12.4)**	22 (48.9)
Physicians	87	25 (28.7)	10 (11.5)	10 (40)
Nurses	82	16 (19.5)	9 (11)	9 (56.3)
Cleaners	9	4 (44.4)	3 (33.3)††	3 (75)

*Includes both methicillin-sensitive *S. aureus* (MSSA) and MRSA.

†Percentage of MRSA among total samples.

‡Percentage of MRSA among *S. aureus* isolates.

§The carriage rate of MRSA among inpatients was significantly higher than among outpatient children (odds ratio [OR]: 4.03, *P* < 0.05).

¶Mothers of inpatient children.

The carriage rate of MRSA among mothers was significantly higher than among outpatient children (OR: 5.50, *P* < 0.02).

**The carriage rate of MRSA among HCWs was significantly higher than among outpatient children (OR: 6.28, *P* < 0.006).

††The carriage rate of MRSA among cleaners was significantly higher than among children, regardless whether they are inpatients or outpatients (OR: 6.81, *P* < 0.003).

children (8.3% versus 2.2%, respectively). More than 70% of inpatient children have associated risk factors and are considered HACO-MRSA cases, which may explain the higher MRSA carriage rate observed among them. A recent study from Cambodia found no significant difference in the MRSA carriage rate among inpatient children (4.1%) compared with outpatient children (3.5%).¹⁵ Fritz and others¹⁶ reported carriage rates of MRSA similar to ours among outpatient children (2.4%). For inpatient children, rates of < 1% and 22% for MRSA have been reported from Switzerland and the United States, respectively.^{17,18}

Few studies examined MRSA carriage in children on admission and at discharge. Milstone and others¹³ found 4.9% of children colonized with MRSA on admission to PICU and only 0.5% of children acquired MRSA colonization in the PICU. We found a higher colonization rate (8.3%) among inpatient children at admission and none of MRSA-negative children on admission examined at discharge were colonized with MRSA. However, this does not exclude that some inpatient children may have acquired MRSA in the hospital, as we did not examine all MRSA-negative children on admission and at discharge.

Huang and others¹⁹ reported PVL genes in 28% (60 of 202) of MRSA isolated from the nares of children between 2 months and 5 years of age presented for a well-child health care visit to several medical centers in Taiwan. In this investigation PVL genes were found in 33.3% (6 of 18) of tested MRSA isolates from inpatient children. The PVL-producing *S. aureus* have been associated with pneumonia, and skin and soft tissue infections that can be serious occurring in previously healthy persons.²⁰ Physicians should suspect PVL-positive *S. aureus* (both MSSA and MRSA) when outbreaks of such infections occur in the community or in healthcare settings.

Interfamilial transmission of MRSA including parent-to-child transmission has been reported previously.²¹ Furthermore, relatives of MRSA carriers may be an important source of MRSA in the community²²; in this study four pairs of a child and concordant mother each were MRSA carriers. Three of these pairs had an identical antimicrobial susceptibility profile and PFGE type. Furthermore, one of these three pairs were also both positive for PVL genes, indicating that at least in this pair intrafamilial transmission may have occurred. However, more studies are needed, with all those living in the household being sampled, to confirm our observation employing a DNA sequencing method such as multilocus sequence typing or spa typing combined with PFGE. Each of the four MRSA isolates from HCWs had a unique antibiotic resistance profile and none of these profiles was similar to those found in MRSA isolates from the four mother-child pairs. This finding indicates that several clones of MRSA may exist in TCH that are different from those isolated from mothers and their children. Furthermore, this indicates that the four mother-child pairs may not acquire their MRSA isolates in TCH. Although three of the inpatient children were classified as HACO-MRSA cases it does not eliminate the role of intrafamilial transmission in the acquisition of MRSA.

Resistance to mupirocin among *S. aureus* (including MRSA) from children with recurrent skin and soft tissue infection has been reported²³; in this study all MRSA isolates were susceptible to mupirocin and vancomycin. On the other hand, we found high resistance rates of MRSA isolates to clindamycin, gentamicin, and fusidic acid including those

isolated from children (30.8%, 42.3%, and 50%, respectively). The observed high rates of resistance to these drugs may require local physicians to limit their use in the treatment of MRSA infections in children in Libya.

Low resistance rates (2.3%) to trimethoprim-sulfamethoxazole among MRSA from children have been reported from Australia.²⁴ On the other hand, a study from Andhra Pradesh, India reported a high resistance rate (67%) among MRSA isolated from the anterior nares of schoolchildren to trimethoprim-sulfamethoxazole.²⁵ None (0.0%) of our MRSA isolates were resistant to trimethoprim-sulfamethoxazole. However, nearly 31% of MRSA from children were resistant to ciprofloxacin. Since the introduction of ciprofloxacin nearly two decades ago in Libya a decline in the use of trimethoprim-sulfamethoxazole and an increase in the use of ciprofloxacin in medical practice in the country were noticed (Ghenghesh KS, unpublished data). This may explain the zero and high resistance rates of MRSA isolates to trimethoprim-sulfamethoxazole and ciprofloxacin, respectively, observed in this investigation. However, our observation does not explain how inpatient children acquired ciprofloxacin-resistant MRSA, as ciprofloxacin and nalidixic acid are not used routinely in the treatment of childhood infections in Tripoli hospitals (Almbrok SO, TCH, personnel communication). We can speculate that interfamilial transmission may play a role in children getting infected with ciprofloxacin-resistant MRSA.

Over the last two decades an increase of CA-MRSA infections have been observed. Strains of CA-MRSA are spreading rapidly in many communities in different regions of the world affecting sick individuals with or without previous contact with a healthcare facility¹; in this investigation nearly 30% of MRSA-positive inpatient children were identified as CA-MRSA cases. Lack of data makes it impossible to comment on the trend of CA-MRSA in the country. We found no significant difference ($P > 0.05$) in detection of PVL genes in CA-MRSA compared with HACO-MRSA isolates. Genes coding for PVL is usually associated with CA-MRSA, however as PVL-positive MRSA clones spread around the world the distinction between what is community and what is hospital acquired is becoming increasingly blurred.

To our knowledge, this the first study to examine the nasal carriage of MRSA in children in Libya. Our findings indicate that nasal carriage of multi-drug resistant PVL-positive MRSA is not uncommon among inpatient children and their mothers in Tripoli with the possibility of intrafamilial transmission of such organisms.

Studies are needed in the future using molecular methods to determine the role of CA-MRSA in inpatient pediatrics and adults. Although vancomycin is the drug of choice in the treatment of infections caused by MRSA in pediatrics, trimethoprim-sulfamethoxazole appears to be a viable option for the treatment of such infections in the country. Pediatricians should be careful in prescribing clindamycin and fusidic acid empirically for treatment of suspected MRSA infections in children and should be guided by the local *S. aureus* antibiograms. Healthcare authorities and related government agencies (e.g., Libyan National Center for Infectious Diseases Control) are urgently required to raise awareness of the importance of good hand hygiene and prudent use of antibiotics among HCWs and members of the community to help prevent the spread of MRSA and other MDR organisms in the country.

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Authors' addresses: Omama H. Al-haddad, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya, E-mail: omama.haddad@yahoo.com. Abdulaziz Zorgani and Khalifa Sifaw Ghenghesh, Faculty of Medicine, University of Tripoli, Tripoli, Libya, E-mails: ghenghesh_micro@yahoo.com and zorgania@yahoo.com. Khalifa Sifaw Ghenghesh's present address is El-Nakheel Compound, Unit 12, El-Sherouk City, Cairo, Egypt.

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