METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CARRIAGE IN INFANTS WITH PROTEIN-ENERGY MALNUTRITION

Laura Florescu¹, Teodora Vremeră², Genoveva Bălănică¹,
Mioara Calipsona Matei³, Luminiţa Smaranda Iancu²
University of Medicine and Pharmacy “Grigore T. Popa”- Iaşi
Faculty of Medicine
1. Discipline of Infant Care,
2. Discipline of Microbiology
3. Discipline of Primary Health Care and Epidemiology

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS CARRIAGE IN INFANTS WITH PROTEIN-ENERGY MALNUTRITION (Abstract) Aim: The aim of the present study was to investigate the frequency of methicillin-resistant S. aureus (MRSA) colonization in infants with protein-energy malnutrition (PEM) and to characterize the antibiotic susceptibility patterns in isolated strains. Material and methods: The study included 123 infants with PEM, admitted to the Paediatric Rehabilitation Department of „St. Mary” Emergency Clinical Children’s Hospital Iaşi, during October 1rst 2010 and August 30th 2011. Nasal, pharyngeal and conjunctival swabs were collected for detection of colonization upon admission and at discharge. Results: The study revealed a high rate of MRSA carriage among infants with PEM (62.60%), most of the isolated strains being multidrug-resistant (86.13%), with additional resistance to aminoglycosides, macrolides and inducible resistance to clindamycin. 88% of colonized infants were nasal carriers. Conclusions: Identification of MRSA carriers permits the implementation of measures that decrease the risk for subsequent infection. Keywords: STAPHYLOCOCCUS AUREUS, MRSA, PEM.

Staphylococcus aureus can cause a wide range of diseases, from local to deep-seated infections, in all age groups, in both hospitals and community worldwide (1). The emergence and spread of multi-drug resistant (MDR) methicillin-resistant S. aureus (MRSA) strains have raised the problem of finding efficient treatment of staphylococcal infections. S. aureus is part of the normal flora in a significant fraction of the healthy population. However, persistent carriers are known to have a higher risk of developing S. aureus infections (2). Nasal colonization with MRSA strains is increased in settings where people are in close contact and neonates and infants are particularly more susceptible to colonization and infection with MRSA, one of the most versatile of childhood pathogens (1, 3, 4). This risk is increased in infants with protein-energy malnutrition (PEM), a potentially fatal nutritional disorder, encountered in children world-wide and often associated with a wide variety of infections (5).

The objectives of this study were to investigate the frequency of MRSA colonization in infants with PEM, to characterize the antibiotic susceptibility patterns in
isolated strains, as well as to evaluate the performance of surveillance through cultures at various body sites for *S. aureus* colonization.

**MATERIAL AND METHODS**

The study included 123 infants with PEM, aged between 5 and 48 weeks, admitted to the Paediatric Rehabilitation Department of „St. Mary” Emergency Clinical Children’s Hospital Iaşi, during October 1st 2010 and August 30th 2011. Of the infants included in the study, 107 were born in maternity (87%), 46 required resuscitation manoeuvres (37,4%), and 53 received complex treatment in Neonatal Intensive Care Unit (43,1%). Nasal, pharyngeal and conjunctival swabs were collected upon admission and at discharge. The samples were subsequently processed at “Grigore T. Popa” University of Medicine and Pharmacy Iaşi, Microbiology Department.

The complete antimicrobial susceptibility patterns were evaluated using disk diffusion method, as recommended by Clinical and Laboratory Standards Institute (CLSI) guidelines 2010. We tested the sensitivity to the following antibiotics: penicillin (P), oxacillin (OX), cephalothin (FOX), clindamycin (CM), erythromycin (E), tetracycline (TE), gentamicin (G), tobramycin (T), kanamycin (K), rifampicin (RIF), trimethoprim / sulfamethoxazole (SXT), fluoroquinolones (FQ), linezolid (LZD) and teicoplanin (TEC). Inducible resistance to CM (iCM) was assessed by double-disk (E and CM) diffusion method (D-zone test). Minimum inhibitory concentrations (MICs) for vancomycin (VA) and OX were determined using E-test method (*bioMérieux*, France). Multi-drug resistance among MRSA was defined as concurrent resistance to three or more non-beta-lactam antimicrobial agents.

**RESULTS**

A total of 114 *S. aureus* strains were isolated from 84 patients (68.29% of the total number of infants) upon admission (52 strains) and at discharge (62 strains), as follows: in 30 infants *S. aureus* was found both upon admission and at discharge, 22 infants carried *S. aureus* only upon admission and in 32 infants *S. aureus* was found only at discharge. In 42 patients *S. aureus* was found only in nasal swabs, in 32 cases nasal and extra nasal carriage was detected, while 10 infants were colonized only extranasally.

Of the total number of *S. aureus* strains, 101 were MRSA (88.59%), isolated upon admission (43 strains), as well as at discharge (58 strains) from 77 infants (62.6% of the total number of infants and 91.66% of colonized infants). Most MRSA strains were isolated from nasal swabs (66.33%).

The sensitivity of 30 µg cephalothin disk testing was 99% when compared to MIC detection. MICs for OX varied between 0.125-256 µg/ml, with a heteroresistance rate of 14.85 % of the total number of strains. A high proportion of strains (42.98%) showed OX MICs of > 256 µg/mL. MICs for VA were in the susceptible range, varying from 0.125 to 2µg/mL. MIC$_{50}$ and MIC$_{90}$ values were as follows: for OX – 64 µg/ml, and > 256 µg/mL respectively, and for VA – 1 µg/mL, and 1.5µg/mL respectively.

Of 101 MRSA strains, 87 were MDR (86.13%). MRSA isolates had additional resistance to aminoglycosides (fenotype KTG – 60 strains and fenotype K – 37 strains), macrolides (93 strains), tetracyclines (82 strains) and iCM (87 strains). Twelve different antibiotic resistance patterns were observed among MRSA isolates,
Methicillin-resistant *Staphylococcus aureus* carriage in infants with protein-energy malnutrition

the most frequent profile being: resistant to KTG, E, iCM, TE and intermediate to DO (32 strains), found upon admission (15/32) as well at discharge (17/32). Among the resistance patterns studied, we noticed the predominance at admission of the profile resistant to K, E, iCM, TE, intermediate to DO (10/17), and the predominance at discharge of isolates belonging to the profile resistant to KTG, E, iCM, TE (11/15).

Methicillin susceptible *S. aureus* (MSSA) showed increased susceptibility to antibiotics compared to MRSA strains, the majority being resistant only to P (9/13), while two of them were also resistant to aminoglycosides and other two were resistant to tetracyclines. Most MSSA strains were detected upon admission (9/13).

All strains were sensitive to LZD, VA, TEC, SXT, FQ, and RIF. There was no case of associated or subsequent staphylococcal infection in colonized infants.

**DISCUSSION**

In our country, the number of infants with PEM remains high due to certain specific situations: tendency to stop breastfeeding precociously, gradually intensified during the last decades; inability to ensure a proper artificial nutrition during the first months of life mainly due to lower revenue; a great number of children from disorganized families or abandoned at birth (6). Their nutritional recovery is a long process which requires continuous medical surveillance in care units and, on the other hand, long-term hospitalization predisposes to infection.

*S. aureus* is an important nosocomial pathogen (7). Colonization with *S. aureus* has been described as a risk factor for infection (8) and seems to be associated with an increased risk of atopic dermatitis in infants, although the latter is still disputed. A study by Lebon *et al.* showed that *S. aureus* colonization at 6 months and frequent colonization in the first year of life are associated with moderate to severe atopic dermatitis, while in a study by Skov *et al.*, no such relation was found (2, 9).

Colonization with MRSA strains poses a greater risk of infection than MSSA colonization and usually precedes invasive infection (7, 8). A study by Davis *et al.* shows that 19% of patients colonized with MRSA at admission and 25% of those colonized during hospitalization developed infection, compared with 1.5% of patients colonized with MSSA and 2.0% of patients uncolonized. MRSA carriage at admission was found to increase the risk of infection, compared with MSSA carriage or no staphylococcal colonization at admission (7). However, according to Fritz *et al.*, MRSA nasal carriage is mostly self-limited, compared to MSSA carriage which seems to be more persistent (10). The anterior nares are the most frequent carriage site (2). It is estimated that 20–40% of healthy individuals are nasal carriers (1). We have evaluated 3 sites for *S. aureus* colonization: nares, oropharynx and conjunctiva. We found that nasal cultures were able to detect carriage in 88% of colonized infants, the rest of the patients being colonized only extranasally. A study by Cursino *et al.* evaluated 4 sites for colonization in newborns from Brazil and concluded that multiple culture sites are needed, a combination of nares and umbilical samples detecting 86% of MSSA and 91% of MRSA colonization cases (11).

The rate of staphylococcal colonization among normal weight children varies greatly with age, being 40 - 50% in newborns.
and infants during the first 8 weeks and falls to 21% by 6 months (11,12, 13) According to Chatzakis et al., the rate of infant carriage in Greece was lower, 17.7% respectively (14). In a study by Sedighi et al., in Iran, 22.5% of children from daycare centres were carriers, but the rate of MRSA colonization was very low (4.1%) (3). In Romania, a study by Constantiniu et al. revealed a rate of S. aureus colonization among children in community of 7.18%, of which only 5.4 % were MRSA (15).

Among our patients, the rate of colonization with S. aureus was very high (68.29%), of which the majority were colonized with MRSA (91.66%).

Persistent colonization poses a higher risk of staphylococcal infections. Children are thought to have higher persistent carriage rates than adults (13), although Lebon et al. dispute that in infant population those carriers are rare (2). Children with persistent staphylococcal colonization often carry identical strains (10). Our study revealed that 8.33% of colonized infants carried S. aureus strains with identical antibiotic resistance patterns upon admission and at discharge, while 27.38% had strains with different resistance profiles which suggest that, in some cases, the source of these strains was the care unit. On the other hand, no case of subsequent infection occurred among infants colonized at admission to the hospital or in those who developed colonization during hospitalization. We note that persistent carriage needs to be evaluated periodically during hospitalization and even after discharge, since, in many cases, transition to intermittent or noncarriage state is possible. The isolation of S. aureus strains in a high percentage of infants after admission to hospital could be explained by the high rate of pathological antecedents together with the immune deficit due to malnutrition, but it could also be caused by close contact during hospitalization or transmission from colonized mothers. In a study by Peacock et al. (UK) the source for infant colonization was usually represented by the mother (12). In our study, staphylococcal colonization in mothers was not investigated.

We appreciate that the increase in MRSA colonization was facilitated by the long hospitalization duration which was needed to improve weight deficit and the acquired immunodeficiency by low nutrient intake.

Infants that were healthy carriers did not receive topical mupirocin ointment because it was not available for purchase.

We emphasize that the sanitary rules have been respected, and we tried to ensure optimal conditions for nursing, in order to limit the involvement of environmental factors in the dissemination of S. aureus. However, we have not managed to maintain, throughout the duration of the study, an effective ratio of staff to children, because of an acute shortage of medical staff.

CONCLUSIONS

We conclude that colonization by S. aureus and MRSA strains is common in infants with PEM hospitalized in Paediatric Rehabilitation Department (68.29% and 62.6%, respectively), much higher compared with studies from other countries, with the major remark that cited studies were about children with normal weight; no subsequent staphylococcal infections were reported. Antimicrobial susceptibility testing revealed a worryingly high rate of multidrug-resistance among MRSA strains.
Methicillin-resistant *Staphylococcus aureus* carriage in infants with protein-energy malnutrition

isolated from colonized infants (86.13%).

Given the age group studied and the antibiotic sensitivity spectrum of MRSA strains isolated, we consider linezolid and vancomycin as therapeutic options in the case of colonized infants that develop subsequent staphylococcal infection; cotrimoxazole can be used in infants older than 2 months, and fluoroquinolones are not recommended because of their adverse effects.

This study highlights the need to improve primary care to ensure an adequate nutritional status of infants, in order to disrupt the vicious circle malnutrition - infection - malnutrition.

Detecting MRSA colonization at admission allows us to identify a high-risk population and facilitates the implementation of strategies for decolonization and reduction of MRSA transmission and infections.

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**REFERENCES**


NEWS

CARDIOVASCULAR EFFECTS OF INTENSIVE LIFESTYLE MANAGEMENT IN PATIENTS WITH TYPE 2 DIABETES

Weight loss and healthy eating are recommended for overweight and obese patients with type 2 diabetes due to the positive effects verified in the short term but long-term cardiovascular effects have not been demonstrated. In 16 U.S.A. centers were randomized 5145 patients with type 2 diabetes, overweight and obese, who received a hypocaloric diet and exercise training (intervention group) versus medical treatment of diabetes (control group). The main objective was to quantify the deaths from cardiovascular causes, cerebral, myocardial infarction, and hospitalization for angina, for a follow-up of 13.5 years. The trial was stopped early, after a period of 9.6 years, as it was reported that, although it was a significant decrease in weight (8.6% vs. 0.7% at one year, 6% vs. 3.5% at the final), the difference in cardiovascular morbidity and mortality was only 403 patients in the intervention group compared to 418 in the control group (p = 0.51). The remaining benefits were significant lifestyle changes: decreased glycosylated hemoglobin, partial remission of diabetes, reduction of urinary incontinence, sleep apnea, depression and quality of life. (The Look AHEAD Research Group, Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes, N Engl J Med 2013; 369: 145-154)

Corina Dima-Cozma