Metisiline Dirençli Staphylococcus aureus Olgularının Değerlendirilmesi

Evaluation of Methicillin Resistant Staphylococcus aureus Infection in Children

Edanur Yeşil, Solmaz Çelebi, Arife Özer, Mustafa Hacımustafaoğlu

Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Enfeksiyon Hastalıkları Bilim Dalı, Bursa

ÖZ

AMAÇ: Bu çalışma, hastanemiz Çocuk Sağlığı ve Hastalıkları Kliniği'nde yatarak izlenen hastalarda metisiline dirençli *Staphylococcus aureus* **(**MRSA) enfeksiyonlu olguların incelenmesi ve ayrıca toplum kaynaklı MRSA'ya dikkat çekmek amaçlı yapılmıştır.

MATERYAL ve METOD: Uludağ Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Kliniği'nde, Ekim 2012-Şubat 2017 tarihleri içerisinde yatmış olan hastalardan alınan kültürlerde *S. aureus* anlamlı üremesi olanlar çalışmaya dahil edildi. İstatistiksel analizlerde SPSS 17.0 programı kullanıldı.

BULGULAR: Bu dönem içerisinde toplam 31 *S. aureus* enfeksiyonu saptandı. *Staphylococcus aureus* enfeksiyonu gelişen olguların 17'si (%54,8) sağlık bakımı ilişkili idi. Sağlık bakımı ilişkili stafilokok enfeksiyonlarının 12'sinde (%70,5) MRSA mevcuttu. Toplum kaynaklı 14 stafilokok enfeksiyonundan 12'sinde (%85,7) MRSA üremesi saptandı. Toplum kaynaklı MRSA enfeksiyonlu olgularının %83'ü (n=10) erkek olup ortalama yaşı 67,6±77,8 ay (medyan 26, aralık 1-204) idi. Sağlık bakımı ilişkili MRSA (SB-MRSA) enfeksiyonlu olguların %67'si (n=8) erkek olup ortalama yaşı 106,7±81,3 ay (medyan 108, aralık 0-222) idi. Toplum kaynaklı MRSA üreyen olgularda ön planda yumuşak doku enfeksiyonu tanısı mevcuttu. Sağlık bakımı ilişkili MRSA olgularında sık görülen etyolojik sebep bakteriyemi idi. Yumuşak doku enfeksiyonlarının %69'u TK-MRSA iken, diğer enfeksiyonların % 73'ü SB-MRSA'dan kaynaklanmaktadır (p=0,041). Olgularda MRSA ilişkili mortalite saptanmamıştır.

SONUÇ: Çalışmamızda toplum kaynaklı stafilokok enfeksiyonlarında MRSA (%85,7) oranı yüksek bulunmuştur. Toplum kökenli MRSA, çoğu durumda yumuşak doku enfeksiyonları ve ardından septisemi ile saptanmıştır. Bakteriyemi, sağlık bakımından edinilen MRSA olgularının başlıca nedeni olmuştur.

Anahtar Sözcükler: Çocukluk dönemi, MRSA, sağlık bakımı ilişkili enfeksiyon, *Staphylococcus aureus,* toplum kaynaklı enfeksiyon.

Sorumlu yazar yazışma adresi: Edanur YEŞİL. Uludağ Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Çocuk Enfeksiyon Hastalıkları Bilim Dalı, Bursa
E-posta:eda_hacettepe@hotmail.com

SUMMARY

BACKGROUND: This study was conducted to investigate cases of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and also to draw attention to community-acquired MRSA in patients hospitalized at our Pediatric Clinics.

METHODS: The patients who had meaningful *S. aureus* growth in the cultures taken from the patients who were hospitalized in Uludag University Medical Faculty Children's Health and Diseases Clinics between October 2012-February 2017 were included in the study. SPSS 17.0 program was used for statistical analysis.

RESULTS: A total of 31 *S. aureus* infections were detected during this period. Seventeen (54.8%) of the cases with *S. aureus* infection were health care related. Methicillin-resistant *S. aureus* was present in 12 (70.5%) of the healthcare-acquired staphylococcal infections. Methicillin-resistant *S. aureus* was detected in 12 (85.7%) of 14 community-acquired staphylococcal infections. Eighty-three percent (n=10) of community-acquired MRSA infections were male and their mean age was 67.6 ± 77.8 months (median 26, range 1-204). Sixty-seven percent (n=8) of healthcare-acquired MRSA (HA-MRSA) were male and their mean age was 106.7±81.3 months (median 108, range 0-222). Most of the community-acquired MRSA patients were diagnosed with soft tissue infection. In the HA-MRSA cases, bacteraemia was the most common infection. Sixty-nine percent of the soft tissue infections originated from CA-MRSA, 73% of the other infections originating from HA-MRSA (p=0.041). MRSA associated mortality was not detected in the cases.

CONCLUSIONS: Methicillin-resistant *S. aureus* (85.7%) was found to be high in community-acquired staphylococcal infections in our study. Most of the community-acquired MRSA was detected in patients with soft tissue infections, followed by septicemia. Bacteraemia was the most frequent healthcare-acquired MRSA infection.

Key words: Community-acquired infections, healthcare-acquired infections, methicillin-resistance, pediatrics, *Staphylococcus aureus*.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to frequently used beta-lactam antibiotics. Methicillin-resistant *S. aureus* was first identified in the 1960s and became the major pathogen in hospitals in the 1980s (1). Methicillin-resistant *S. aureus* is an important factor in healthcare-acquired infections, especially in hospitalized patients. In recent years, community-acquired MRSA (CA-MRSA) infections are seen in patients without a healthcare-related risk factor. The methicillin resistance in *S. aureus* is defined as the minimum inhibitor concentration (MIC) of oxacillin ≥4 mcg/mL. Community-acquired MRSA infection most commonly causes skin and soft tissue infections; it may also cause necrotizing pneumonia, sepsis and osteoarthritis. Community-acquired MRSA strains are endemic in many communities and differ from other genetically defined MRSA strains. Community-acquired MRSA is more pathogenic than other *S. aureus* strains (2), (3), (4).

Patients who developed MRSA infections typically had the following risk factors; surgery, dialysis, hospitalization; indwelling percutaneous devices such as central venous catheters or feeding tubes, or the patient had previous MRSA infection proven by culture. Healthcare-acquired MRSA infection is defined as MRSA infection which develops 48 hours after hospitalization (2).

Community-acquired MRSA is considered as a risk group for those who are detained at the correctional institution, children staying in the homeland, homosexual relations, military personnel, athletes, Native Americans, people with low socioeconomic status, and young children. However, since CA-MRSA strains are endemic in many parts of the world, it is known that almost every person can develop a CA-MRSA infection (2).

This study was carried out to investigate cases of MRSA infections in patients hospitalized in our Hospital for Children's Health and Diseases and also to draw attention to community-acquired MRSA.

MATERIALS and METHODS

This is a retrospective study in a tertiary hospital. The patients who had meaningful *S. aureus* growth in the cultures taken from the patients who were hospitalized in Uludag University Medical Faculty Children's Health and Diseases Clinics between October 2012-February 2017 were included in this study. We used the definitions of Centers for Disease Control and Prevention in this study. Healthcare-acquired MRSA infection was defined as MRSA infection that developed 48 hours after hospitalization. Methicillin-resistant *S. aureus* infections in patients without MRSA colonization and no recent hospital admission were considered community-acquired. Bacterial identification and

antibiotic susceptibility tests were done in BD Phoenix 100 (Becton Dickinson, USA) system. Methicillin resistance tests were repeated according to Clinical and Laboratory Standards Institute (CLSI) recommendations by cefoxitin disc in the Kirby Bauer disc diffusion method (5). SPSS 17.0 program was used for statistical analysis. Chi-square test was used at the table-1 and a P-value of less than 0.05 was considered significant**.**

RESULTS

During this period, a total of 31 *S. aureus* infections were detected. Seventeen (54.8%) cases of *S. aureus* infection were related to health care. Methicillin-resistant *S. aureus* was present in 12 (70.5%) of the healthcare-acquired staphylococcal infections. Methicillin-resistant *S. aureus* was detected in 12 (85.7%) of 14 community-acquired staphylococcal infections (Figure-1).

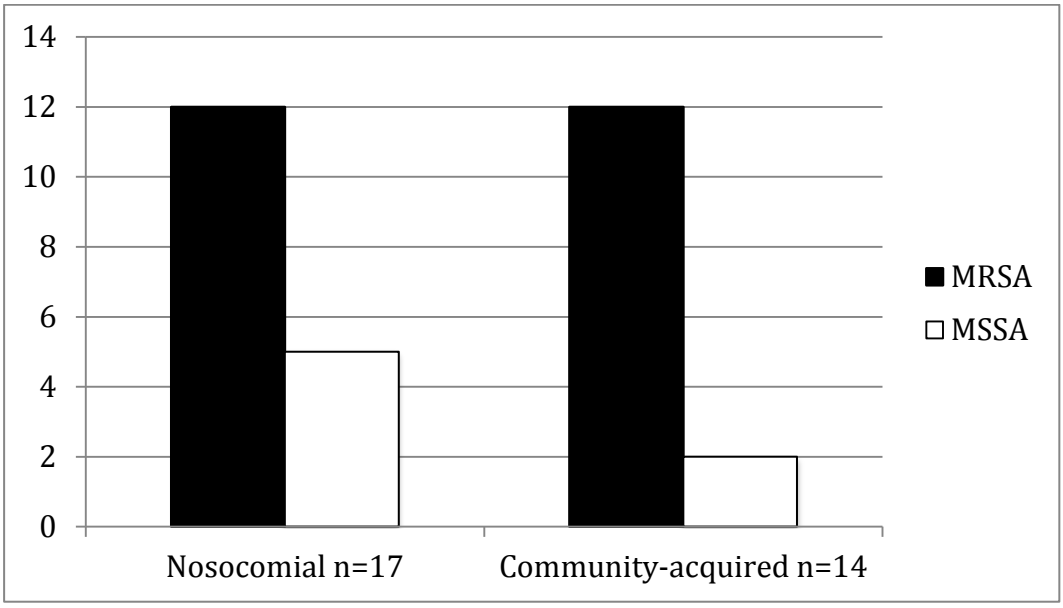

Figure-1: Distribution of healthcare-acquired and community-acquired *S. aureus* infections.

Eighty-three percent (n=10) of CA-MRSA infected cases were male and their mean age was 67.6±77.8 months (median 26, range 1 to 204 months). Sixty-seven percent (n=8) of HA-MRSA infected cases were male and their mean age was 106.7±81.3 months (median 108, range 0-222 months). There were no significant sociodemographic or characteristic (e.g. age, hospital stay, underlying disease) differences between the two groups.

Community-acquired MRSA was detected in 9 (76%) wound, 2 (16%) peripheral blood and 1 (8%) pericardial fluid culture. There were 2 bacteriemia, 1 pericarditis, and 9 soft tissue infections in CA-MRSA producing cases (Table 1).

Healthcare-acquired MRSA was detected in 5 (43%) peripheral blood, 4 (33%) wound, 2 (16%) endotracheal aspirate, and 1 (8%) central line blood culture. There were 6 bacteremia, 2 pneumonia, 4 soft tissue infections in HA-MRSA-producing cases (Table 1).

Table 1. Distribution of methicillin-resistant *Staphylococcus aureus* (MRSA) infections

Infection site	**CA-MRSA n=12**	**HA-MRSA n=12**
Soft tissue infections, n (%)	9 (75)	4 (33.3)
Bacteriemia, n (%)	2 (16.6)	6 (50)
Pneumonia, n (%)	0	2 (16.7)
Pericarditis, n (%)	1(8.4)	0

Abbreviation: CA-MRSA, community-acquired methicillin-resistant Staphylococcus aureus; HA-MRSA, healthcare-acquired methicillin-resistant Staphylococcus aureus.

Sixty-nine percent of the soft tissue infections originated from CA-MRSA; 73% of the other infections originating from HA-MRSA (p=0.041). There were 3 (25%) cases of immunodeficiency as the underlying disease in CA-MRSA cases. These were leukocyte adhesion defect, chronic granulomatous disease, and hypogammaglobulinemia. All the 3 cases had skin and soft tissue infections. The most common underlying diseases in HA-MRSA were malignancies (3 acute leukemia, 2 solid tumors), followed by neurologic diseases in 4 cases, congenital heart disease in 1, chronic kidney failure in 1, vehicle-related traffic accidents in 1. Similar treatments were used in both MRSA groups and the treatment was successful. MRSA-associated mortality was not observed in the cases.

DISCUSSION

Methicillin-resistant *S. aureus* rates have been increasing worldwide since the 1990s (6). Today, broad-spectrum antibiotics, invasive procedures, and surgical interventions are the main causes of MRSA outbreaks. Patients infected and colonized with methicillin-resistant *S. aureus* become important reservoirs for health care-acquired infections. This condition could cause epidemics in neonatal intensive care units (7). It has been reported that CA-MRSA is more virulent than HA-MRSA and its morbidity and mortality are considerably high (2, 8). Community-acquired MRSA is the most commonly seen in skin and soft tissue infections (abscess, froncule), although it can cause severe

diseases such as sepsis, osteomyelitis, and pneumonia. Healthcare-acquired infections can cause prosthetic joint infection and surgical site infections (9), (10).

In this study, 14 (45.2%) of *S. aureus* infections originated from the community and the MRSA rate was 85.7%, which was significantly higher than our previous study in 2007 (11). In 2013, 50.4% of the 31,448 MRSA patients who received inpatient treatment in California were identified as CA-MRSA. The proportion of CA-MRSA to total MRSA cases is 1-2% in Spain and Germany, and 29-56% in Denmark and Sweden. This rate was found to be 6% in the Italian Ligurian region, 14% in Germany, 18% in France, and 30% in Greece, in the case of outpatients (12). In a study examining the MRSA strains in skin and soft tissue infections in Turkey, out of 30 MRSA strains, 93.3% (n=28) were related to health care and 6.7% (n=2) were related to community (13). In this study, we found that 17 (54.8%) cases of *S. aureus* infections were related to health care, and this rate was lower than our previous study (11). In this study, MRSA was present in 12 (70.5%) of the healthcare-acquired staphylococcal infections. Our previous study demonstrated a methicillin resistance rate of 25.2% (75/297) in nosocomial *S. aureus.* The proportion of MRSA significantly increased from 18.9% during January 1997 – June 2000 to 32.4% during July 2000 – January 2004. This rate was higher than our previous study (11).

In a surveillance study conducted on three different populations in the USA, skin and soft tissue infections were the most common findings of CA-MRSA disease (77%) followed by wound infection (10%), urinary tract infection (4%), sinusitis (% 4) and pneumonia (2%) (4). Our results were similar. In another multicenter study, *S. aureus* was the most common cause of skin and soft tissue infections in emergency department patients (14). In this study, soft tissue infections (75%) were the most common infection, followed by bacteriemia (16.6%) and pericarditis (8.4%) in patients with CA-MRSA. In another study, among the patients with community-acquired skin and soft-tissue infections due to *S. aureus*, CA-MRSA was responsible in 63% (244 out of 389) and methicillin-sensitive *S. aureus* (MSSA) caused 28% (110 out of 389) (15).

Bacteremia is frequently observed in patients with HA-MRSA infection (3, 10). Similarly, bacteremia was the most frequent infection (50%) in our study, followed by soft tissue infections (33.3%) and pneumonia (16.7%). In this study, 69% of the soft tissue infections originated from CA-MRSA whereas 73% of the other infections originated from HA-MRSA, and this difference was statistically significant (p=0.041).

Methicillin-resistant *S. aureus* associated mortality was not observed in our study. The mortality rate in *S. aureus* bacteremia varies between 30-40% (16). In bacteremia patients, the 30-day mortality odds ratio of MRSA to MSSA was 2.15 (17).

In conclusion, there is an increase in MRSA infections. In our study, especially the community-acquired MRSA rate was found to be high. This result deserves attention despite the low number of patients in our study. For Turkey, more clinical trials are needed to determine the different genetic and clinical characteristics of CA-MRSA and HA-MRSA.

Conflict of interest: The authors declare no conflict of interest.

Author contribution: E.Y. and S.Ç. designed and wrote the study, A.Ö. collected and analysed data. M.H. gave technical support and conseptual advice. All authors read and approved the final manuscript.

REFERENCES

1. Jevons MP, Coe AW, Parker MT. Methicillin resistance in staphylococci. *Lancet*. 1963;1(7287):904-7.

2. Patel M. Community-associated meticillin-resistant Staphylococcus aureus infections. *Drugs*. 2009(69.6):693-716.

3. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *JAMA*. 2007;298(15):1763-71.

4. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al. Methicillin-resistant Staphylococcus aureus disease in three communities. *N Engl J M*. 2005;352(14):1436-44.

5. Wayne PA. Performance standards for antimicrobial susceptibility testing. *Clinical and laboratory standards institute*. 2012(22nd Informational Supplement):M100- S22.

6. de Kraker ME, Davey PG, Grundmann H, group Bs. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS Med*. 2011;8(10):e1001104.

7. Agca H, Topac T, Ozmerdiven GE, Celebi S, Koksal N, Hacimustafaoglu M, et al. Investigation of methicillin resistant Staphylococcus aureus in neonatal intensive care unit. *Int J Clin Exp Med*. 2014;7(8):2209-13.

8. Etienne J. Panton-Valentine leukocidin: a marker of severity for Staphylococcus aureus infection? *Clin Infect Dis*. 2005;41(5):591-3.

9. Benoit SR, Estivariz C, Mogdasy C, Pedreira W, Galiana A, Galiana A, et al. Community strains of methicillin-resistant Staphylococcus aureus as potential cause of healthcare-associated infections, Uruguay, 2002-2004. *Emerg Infect Dis*. 2008;14(8):1216-23.

10. Sutton JP, Steiner CA. Hospital-, Health Care-, and Community-Acquired MRSA: Estimates From California Hospitals, 2013: Statistical Brief #212. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD)2006.

11. Celebi S, Hacimustafaoglu M, Ozdemir O, Ozakin C. Nosocomial Gram-positive bacterial infections in children: results of a 7 year study. *Pediatrics Int*. 2007;49(6):875-82.

12. Kock R, Becker K, Cookson B, van Gemert-Pijnen JE, Harbarth S, Kluytmans J, et al. Methicillin-resistant Staphylococcus aureus (MRSA): burden of disease and control challenges in Europe. *Euro Surveill*. 2010;15(41):19688.

13. Baran CB. Investigation of Panton-Valentine leukocidin gene, SCCmec gene cassette types and genotypes of methicillin-resistant Staphylococcus aureus strains isolated from outpatients. *Mikrobiyol Bul*. 2010;44.4:533-45.

14. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. *New Engl J M*. 2006;355(7):666-74.

15. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med*. 2006;144(5):309-17.

16. Kaku N, Yanagihara K, Morinaga Y, Yamada K, Harada Y, Migiyama Y, et al. Influence of antimicrobial regimen on decreased in-hospital mortality of patients with MRSA bacteremia. *J Infect Chemother*. 2014;20(6):350-5.

17. Lawes T, Edwards B, Lopez-Lozano JM, Gould I. Trends in Staphylococcus aureus bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis. *BMJ Open*. 2012;2(3).