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Mini Review

THE STAPHYLOCOCCI SPECIES IN THE HUMAN ECOSYSTEM AND AS PATHOGENS OF HEALTHCARE – ASSOCIATED INFECTION

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ABSTRACT

The human body, in its evolution, has developed as a distinct, stable ecosystem with established relationships of synergy and commensalism with the microorganisms residing within it. Staphylococci are an integral, structural-defining part of the human microbiome. Their nasal localization becomes a primary reservoir that, in hospital settings, supports the mechanism of spread and poses a risk to susceptible patients. Control of nasal staphylococcal colonization among staff in high-risk departments of general hospitals has shown, in recent years, a predominant presence of methicillin-resistant coagulase-negative staphylococci (CNS-MR), with a high epidemic potential. In the etiological aspect, we observe a decrease in the relative share of *Staphylococcus aureus* as a causative agent of healthcare-associated infections (HAI) from 73.42% in 2008 to 11.76% in 2022. Conversely, the frequency of infections associated with coagulase-negative staphylococci (CNS) has increased, from 26.58% at the beginning of the observation period to 88.24% in 2022. The proportion of methicillin-resistant coagulase-negative staphylococci (CNS-MR) has also risen as part of all multi-drug-resistant bacterial species isolated from clinical samples. Strains with this type of resistance are primarily found in patients who have undergone surgery, with localization at the surgical site.

In order to ensure the safety of patients treated in the hospital, we share the opinion on the necessity of continuous infection control for both patients and staff, accurate microbiological diagnostics, and the development of an effective strategy for the treatment and prevention of staphylococcal nosocomial infections and carriage

Keywords: healthcare-associated infections (HAI), nasal staphylococcus carriers, Staphylococcus aureus, coagulase-negative staphylococci (CNS), methicillin-resistant strains (MR).

INTRODUCTION

The human body, along with the microorganisms adapted to live within it, as resident, permanent flora, represents a unique ecosystem. Relationships typical of parasitic systems—commensalism, synergy, and antagonism—are established among the microorganisms within it. The quantity and composition of the microbiota vary depending on the anatomical site and the stability of the entire community. Often, within a single microbial family, both resident and pathogenic forms can be found simultaneously due to the presence of some common characteristics—biochemical, antigenic, and others (1-3).

Staphylococci are an integral and significant part of the human natural microbiome, with primary localization on the skin and mucous membranes. The most common site of mucosal colonization is the vestibulum nasi, which is also their main reservoir for spread (4). Nasal colonization with *Staphylococcus aureus* begins in the first days after birth, with the primary source being the mother. By the end of the second month, staphylococcal carriage is found in about 50% of newborns, after which it starts to decrease and reaches about 20% by the sixth month (5-7).

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In the subsequent periods of life, carriage is mainly maintained through contact with the environment, via the vector—contaminated hands (8).

The other major group is *coagulase-negative staphylococci* (CNS), defined by the main differentiating feature—coagulase production, introduced in 1940 by Fairbrother RW. According to recent studies, they are grouped into 38 taxonomic species. In humans, they are primarily found as commensals, most commonly in the moist areas of the skin and the anterior parts of the nose. In the nasal microbiome of adults, CNS most often coexist with *Staphylococcus aureus* and representatives of the *Corynebacterium* and *Propionibacterium* genera (9-11).

The mechanisms of nasal staphylococcal colonization have been the subject of extensive and in-depth research. The first stage in the realization of this process is bacterial adhesion to the cells of the nasal mucosa. The attachment of staphylococci is primarily facilitated by elements of the extracellular matrix—fibrinogen, fibronectin, and collagen (12-15). Collagen-binding protein is another important adhesive component, which is defined as a genetically determined factor (13, 16). Important participants in the process of attachment to the epidermis are the staphylococcal surface proteins—loricrin, cytokeratin 10 (K10), involucrin, filaggrin, and others. Results from studies by various authors highlight the significance of the expression of adhesive molecules by *Staphylococcus aureus*, as well as the involvement of the staphylococcal non-protein adhesive—teichoic acid (16-19).

Several analyses identify staphylococcal protein A (SpA) and the exoprotein staphylokinase as key factors for bacterial adaptation to the host's immune system in the establishment of staphylococcal carriage (20, 21, 11). Biopsy studies of the vestibulum nasi in healthy individuals have revealed the intracellular presence of *Staphylococcus aureus* in the cells forming the epidermis (22). The hiding of staphylococci in epithelial, endothelial, and adipose cells is an additional factor that provides them with a good protective effect against the host's defense mechanisms and explains the failure of local and systemic antimicrobial agents, antiseptics, as well as cases of recolonization in some healthy carriers (23-27).

Nasal staphylococcal carriage is one of the important and primary reservoirs for their preservation and provides the potential for intensive spread in hospitals. Therefore, it is subject to constant monitoring, both among healthcare personnel and at-risk patient groups.

AIM

In this study, we examine the role of staphylococci within the human ecosystem and assess their significance as etiopathogens of nosocomial infections in a hospital setting. As an important aspect of infection control for this type of infection, we emphasize the necessity of conducting systematic monitoring of staphylococcal nasal carriage among high-risk patient groups and healthcare personnel, as well as monitoring elements of the hospital environment involved in the epidemic process. The discussion of risk factors is supported by the results of our studies conducted at the Multi-Profile Hospital for Active Therapy "St. Anna – Varna.

Staphylococcal carriage among healthcare personnel – results from our own studies in high-risk departments in Multi-Profile Hospital for Active Therapy "St. Anna – Varna"

Over a period of one year, 4 mandatory screenings of the staff were conducted, along with three follow-up tests to identify persistent carriers in the high-risk departments of the general hospital.

The summarized results show:

Intensive Care and Resuscitation Department:

- Among doctors – 47.62% transient carriage of **CNS-MR**;
- Among nurses – 25.81% transient and 22.58% persistent carriage of **CNS-MR**, with mupirocin resistance confirmed in 2 cases;
- Among orderlies – 80% are transient carriers, and 20% are persistent carriers of CNS-MR, with mupirocin resistance.

Dialysis Treatment Department:

- Among doctors – 1 persistent carrier of **CNS-MR** and 1 of *St. aureus* were identified;
- Among nurses – 77.78% have transient and 22.22% persistent carriage of **CNS-MR**, with mupirocin resistance;
- Among orderlies and technical staff, 1 (14.28%) has transient and 2 (28.57%) have

persistent carriage of **CNS-MR**, with mupirocin resistance.

From the surgical departments, in the *Orthopedics and Traumatology clinic*, after screening the entire staff over a period of one year, the microbiological screening showed: 1 persistent carrier of *St. aureus* and 1 of **CNS-MR** among the doctors; 2 persistent carriers of **CNS-MR**, with mupirocin resistance, among the nurses; and 1 transient carrier of **CNS-MR** among the orderlies.

In a comparative context, a similar study of ours from 2007, conducted in the same departments, showed that in all cases of transient and persistent carriage among the staff, only highly sensitive strains of *St. aureus* were detected. Now, the obtained results convincingly demonstrate a changed profile of nasal colonization, with a dominant presence of resistant strains, coagulase-negative staphylococci (**CNS-MR**), some of which are mupirocin-resistant. This compromises its use as a preventive measure against such forms of staphylococcal colonization. It creates a real condition for the formation of ***reservoirs of resident carriers of CNS-MR*** staphylococci, with a high epidemic potential among the staff, who represent a constant source of infection for patients in these departments.

For many years, the detection of CNS in nasal secretions from at-risk healthcare personnel was considered a normal finding. However, today, their widespread presence in hospital environments and among carriers, along with the acquisition of methicillin resistance and the potential for multiple drug resistance, makes this group a serious risk factor for the development of an epidemic process in the hospital setting. Published studies, starting as early as 1980, have highlighted the high relative proportion of methicillin-resistant isolates of *St. haemolyticus* and *St. epidermidis*. This is confirmed by the results of a 20-year study in Switzerland, which reports that by 2005, cases of isolated CNS-MR in burn patients increased from 11% to 55%, with the resulting risk of hospital-wide transmission (28, 29).

As prophylactic agents used for nasal decolonization in cases of permanent carriage, several antiseptics have been established in medical practice - hibitan-gluconate, Octenisept, pyoctanin, tripaflavin, which show uncertain results. One of the reliable topical agents is Muprocin (Bactroban), which achieves high effectiveness in sensitive variants of St. aureus. From 93 to 99% /-/ results were reported after therapy. However, a number of studies have pointed to the return or recolonization of staphylococci in about 86% of resident carriers (30, 31).

Studies on its effect on CNS do not provide convincing evidence for elimination, and here the issue of mupirocin resistance arises, which practically excludes it as a reliable sanitizing agent. Several authors report increasing resistance to the drug, mainly due to its widespread use in hospitals (32, 33). The issue of *'mupirocin resistance'* is important for practice and should be considered both in its microbiological aspect-testing and proving the antimicrobial sensitivity of the isolates and in an epidemiological context-determining the infection risk for vulnerable patient groups and healthcare personnel (34, 35). In such cases, measures to prevent the epidemic process in the hospital environment should focus on the spatial isolation of the sources of infection and the mandatory use of personal protective equipment by the staff—face masks and gloves—when serving patients, ensuring their periodic change. The application of antibiotics may have a good, immediate effect, but as a systemic practice, it is inappropriate and even dangerous, as it creates conditions for the development of polyresistant hospital strains of staphylococci. It is widely accepted that healthy staphylococcal carriers among staff and patients are their primary reservoir, which maintains their constant circulation in healthcare facilities. Patients in surgical departments, dialysis units, intensive care units, maternity, and neonatal departments are at the highest risk for developing nosocomial staphylococcal infections. Another important group of patients that should be monitored includes those with implanted devices, prosthetics, and implants, where the main problem is the formation of bacterial biofilm. As early as 1984, Peters and Pulverer described infections associated with biofilm, calling them „*chronic infections associated with polymer"* (36). The ability to form multilayered biofilms is an important factor in the pathogenesis of foreign body-associated infections, and it is based on two main properties—adhesion and the accumulation of layers of cells on surfaces. The adhesion phase is coordinated by surface proteins, while the cell accumulation phase

involves not only proteins but also extracellular polysaccharides, with a leading role for glucosamine. These characteristics have been described both in *St. aureus* and in certain strains of coagulase-negative staphylococci (37-40).

Staphylococci are typically leading Gram-positive bacterial pathogens that participate as causative agents of ***healthcare-associated infections (HAIs)*** in all areas of medical practice. Nasal staphylococcal colonization is their primary localization, with the potential for spread in the hospital environment. Immunocompromised, comorbid patients, those with implanted devices, and patients undergoing dialysis are most at risk for developing infections. Staphylococcal nosocomial infections in surgical patients are a serious problem. The risk factors for infection at the surgical site can be defined as complex. The leading risk localization—nasal colonization of the pathogen in patients and staff—is confirmed by Perl et al., 2002, who report an 80% correlation between the infecting agent and that from the nose of the affected patient (41). For orthopedic patients with implants, preoperative screening for nasal carriage is an important preventive measure due to the high risk of postoperative infection associated with implant biofilm (42). Other authors also report an increased frequency of postoperative staphylococcal infections at the surgical site, ranging from 3 to 11 times higher among orthopedic patients (43, 44).

Results from a study on staphylococcal nosocomial infections in Multi-Profile Hospital for Active Therapy "St. Anna – Varna" for the period 2008 – 2022 (own study)

The registration of staphylococcal nosocomial infections, monitored from 2008 to 2022, shows a constant level of morbidity, with a relative share ranging from 9.84% to 23.81%. **(Figure 1)** A similar average relative share of 18.17% is reported in a previous study for the period 2000 – 2004. In an etiological aspect, *St. aureus* shows a tendency to decrease in recent years, with a relative share of 73.42% in 2008, decreasing to 11.76% in 2022. The involvement of CNS as causative agents of healthcare-associated infections (HAIs) is becoming increasingly significant. Their relative share increased from 26.58% to 88.24% by 2022. (**Figure 2)** Until recently, the isolation of this type of staphylococci from clinical materials was considered as contaminant flora. The literature data and our observations confirm their significant role as etiopathogens of a wide range of nosocomial infections and the increase in cases with confirmed methicillin-resistant forms of CNS-MR (45, 46). Staphylococcal infections caused by methicillin-resistant *St. aureus* (MRSA) show a declining trend, with a relative share of under 5.0%, while the share of CNS-MR has gradually increased as part of all multi-drug resistant bacterial species isolated from clinical materials. Since 2017, our analysis has reported the involvement of CNS-MR in hospital infection pathology as an important nosocomial pathogen with a serious resistant potential. The CNS species, burdened with polyresistance, has maintained a consistently high level over the past five years, around or above 20%, reported as a share of the laboratory-detected "pan-drug resistant" bacterial strains in the hospital. **(Figure 3)**

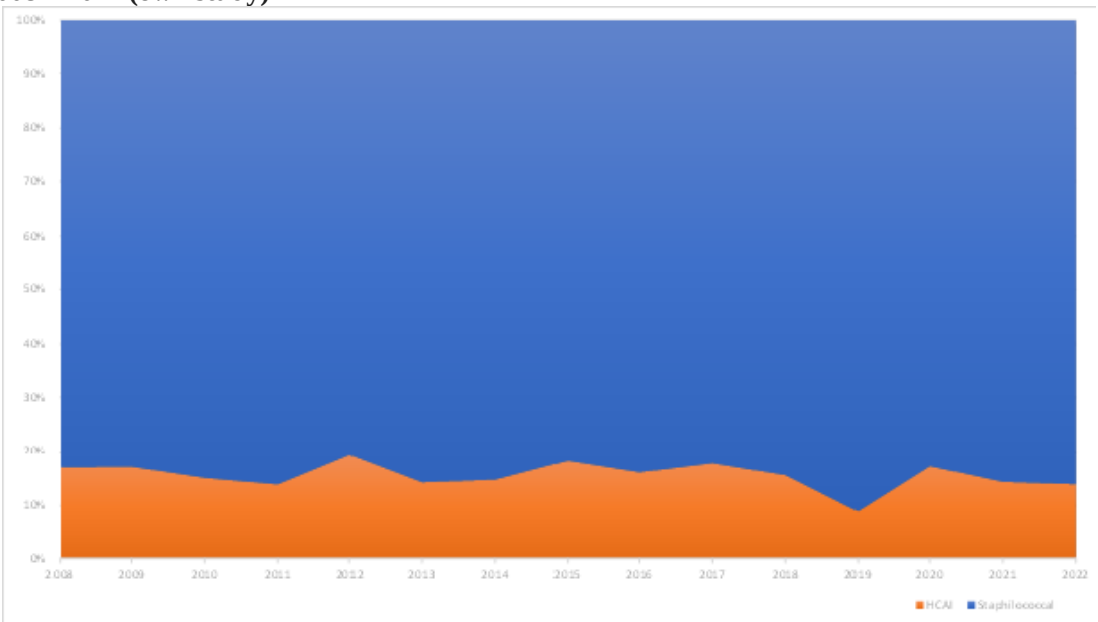

Figure 1. Relative share of nosocomial infections with staphylococcal etiology compared to all diagnosed for the period 2008-2022 in Multi-Profile Hospital for Active Therapy "St. Anna – Varna"

Figure 2. Relative share of nosocomial infections associated with St. Aureus and CNS occurring in in Multi-Profile Hospital for Active Therapy "St. Anna – Varna" for the period 2008-2022

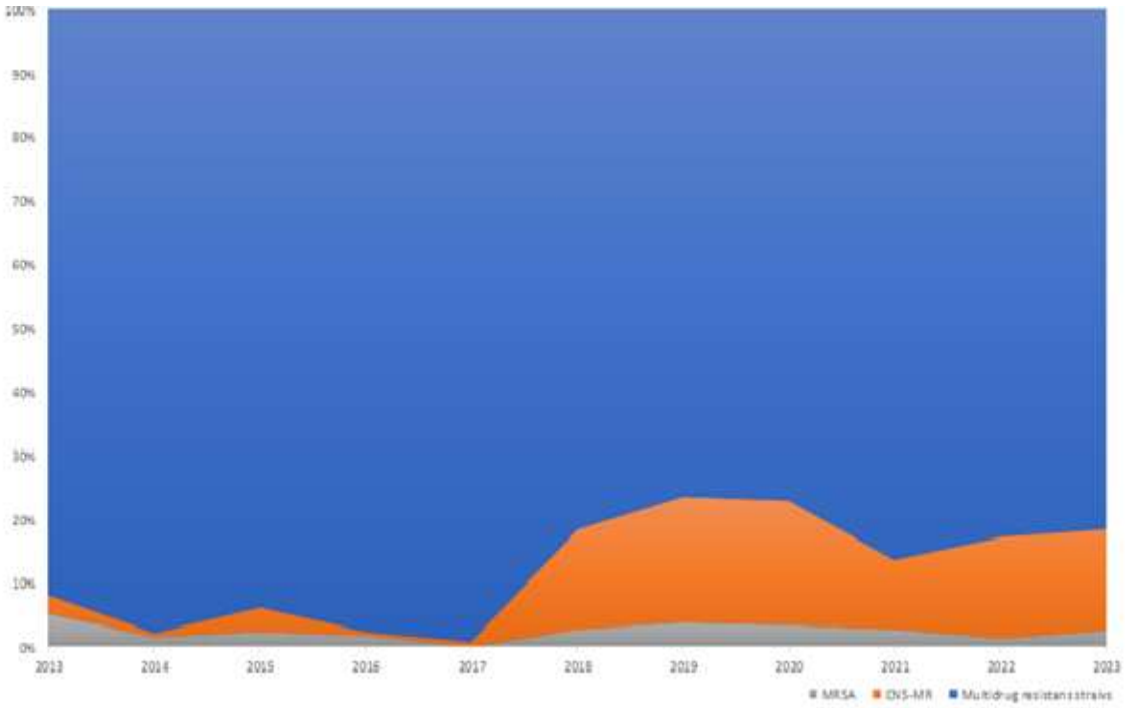

Figure 3. Relative share of CNS-MR and MRSA compared to all multidrug-resistant isolates from clinical materials of patients with HAI, for the period 2013-2023

Among all studied staphylococcal healthcare-associated infections (HAIs), they are primarily found in surgical patients undergoing surgery, with their main localization being the surgical site. Here too, the predominant pathogens responsible for the development of the infectious process are methicillin-resistant CNS. Since 2018, they have been continuously isolated from wound secretions, with a relative

share between 47.41% and 79.45%, and have become the leading etiological factor for the development of surgical site infections.

The summarized epidemiological data and analysis for a period of 15 years provide grounds for considering staphylococcal infections as an important part of nosocomial pathology. Their high frequency and the potential for more effective epidemic spread in hospital wards are linked to various factors: the high resistance of the pathogen in the external environment, the presence of persistent staphylococcal carriers as reservoirs, increased susceptibility among immunocompromised patients, gaps in the hygiene and disinfection protocols, and improper antibiotic policies. Infections associated with CNS most commonly occur through contact transmission, which is facilitated by their widespread presence in the hospital environment. Several proven virulence factors support the infection mechanisms, including genomic flexibility and adaptability, the ability to form biofilm, acquisition of broad antibiotic resistance, and the uncertain effectiveness of Mupirocin in nasal colonization (47-49).

CONCLUSION

Studies by many authors, as well as our own, conducted in a hospital environment, provide grounds to classify CNS as successful pathogens in certain risk groups of patients – those who are operated on, immunocompromised, or have medical devices or implants. Nasal decolonization should be established as a mandatory measure for patients undergoing orthopedic and cardiothoracic surgeries. The spread of multidrug-resistant strains of MRSA and CNS-MR in hospitals poses a risk to patient safety, which is why constant infectious control, accurate laboratory identification, and an effective therapy and prevention strategy are essential.

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