

RISK FACTORS IN SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

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Abstract. Prospective study aimed at establishing the incidence of sepsis with oro-maxillofacial portal of entry and of the causal relationship between the disease and the incriminated risk factors (factors in the living environment, collectivity, occupational environment, behavioral factors). The study group included 200 patients admitted to the Oro-Maxillofacial Surgery and ENT Clinics of the Iasi "St. Spiridon" Emergency Hospital in the interval 2012-2015. *S. aureus* was the main causal agent incriminated in the development of oro-dental sepsis, about ½ of the isolates strains being methicillin-resistant. Age under 50 years, male gender, urban, immunosuppression, recent medical history (previous hospitalization and antibiotic therapy) were significantly correlated with the oral-maxillofacial involvement, which draws attention on the outpatient follow-up of moderate and severe oral infections. The insidious onset described in 54.6% of patients did not raise the suspicion of a potentially life-threatening disease, such as sepsis, but the severe respiratory (43.1%) and neuromeningeal manifestations (25.7%) contributed to the early seeking of expert advice from an infectious diseases specialist. Over 92% of the study patients were at high risk for staphylococcal infection with multidrug-resistant (MDR) strains, significantly more common in men and in patients in whom MRSA was identified as the sepsis pathogen. Depending on the MDR agent involved in the causation of oral-maxillofacial sepsis, the risk of developing severe infections is attributable to methicillin-resistant *Streptococcus mutans*, *Streptococcus anginosus*, *S. epidermidis*, *P. aeruginosa*, *Klebsiella*, β-hemolytic streptococcus, and *Streptococcus salivarius*.

INTRODUCTION

The etiologic spectrum of potentially severe infections has expanded considerably in recent years due to the inadequate administration of antibiotic therapy, widespread use of invasive medical maneuvers, improved techniques for identifying infectious agents, increasing life expectancy and immunosenescence. Of the frequently involved pathogenic microorganisms, Gram-positive bacteria (especially staphylococci) currently rank first (Zinderman C., et al., 2004), followed by fermenting (*E. coli*, *P. aeruginosa*, *Proteus*) and non-fermenting Gram negative bacilli (*Acinetobacter*) and fungi (mainly *Candida* species).

In some epidemiological conditions the colonizing staphylococcal strains may become responsible for the occurrence of a variety of diseases: from localized infections to severe forms of sepsis. Polymorphism and the lack of specificity of symptoms make it difficult to differentiate between different disease categories and create an inventory of associated comorbidities. Within this context, a thorough history and physical exam provide additional information for identifying the patients at risk.

The favorable course of the disease depends on the early etiologic diagnosis and initiation of appropriate therapy. Considering these aspects, current research is aimed at developing new laboratory techniques to reduce the time required for the isolation of infecting strains and performance of antibiotic susceptibility testing. The alarming increase in the rate of resistant staphylococci also requires a constant re-evaluation of the treatment regimens used. In immunosuppressed patients the emergency care consists in both the control of infectious process and correction of associated imbalances (treatment of the underlying diseases) (Elliott R.A., et al., 2010; Singer A.J., et al., 2014).

Implementation of global strategies to prevent of bacterial infections continues to provoke much controversy. Data in the literature on risk factors and management options are limited and often difficult to interpret (Bratzler D.W. & Houck, P.M., 2004; Granny G., et al., 2007; Antibiotic Expert Group, 2010).

Today, one of the major issues facing clinicians is resistance to methicillin of *S. aureus* strains and coagulase-negative staphylococci, which was subsequently extended to other antibiotics. If in the past staphylococcus was regarded as "exclusively nosocomial pathogen" currently we are witnessing the emergence of community-acquired panresistant strains (Kuriyama T., et al., 2005; Nathwani D., et al., 2008; Klevens M., et al., 2006).

PURPOSE AND OBJECTIVES

The aim of this study was to establish a series of correlations between elements of epidemiology and diagnosis of sepsis with oral-maxillofacial portal of entry, highlighting the commonly found risk factors; to describe the clinical course particularities depending on the pathogenic mechanism, associated comorbidities, seeking medical advice, how early diagnosis was made and treatment initiated; study of the clinical course of sepsis, by checking the correlation between the causal agents involved and poor prognosis; selection of a therapeutic regimen according to the local resistance pattern, relying on the best evidence for susceptibility testing; exploitation of the results will lead to a proposal for an effective screening methods in order to reduce morbidity and mortality from sepsis with oral-maxillofacial portal of entry.

MATERIAL AND METHODS

Prospective study conducted in a sample of 200 patients admitted to the Oro-Maxillofacial Surgery and ENT Clinics of the Iasi "Sf. Spiridon" Emergency Hospital in the interval 2012-2015. **Inclusion criteria:** age over 18 years; diagnosis confirmed by positive findings on clinical exam, laboratory tests (bacteriological, hematological, biochemical) and imaging. The strains were isolated from different biological or pathological products: blood (42%), cerebrospinal fluid (25.7%), urine (5.5%), sputum (3.2%), pus (5.3%) or seeding on catheters (5.7%). To assess the risk of infection with MDR staphylococcus strains Carmeli score was used and the patients were stratified into three risk groups: **low risk** (Carmeli score 1- community-acquired infection) - 7 patients (63.6%); **medium risk** (Carmeli score – healthcare-associated infection) - 1 patient (9.1%); **severe risk** (Carmeli score 3 - nosocomial) - 3 patients (27.3%).

For the statistical analysis both descriptive and analytical methods were used, at 95% significance threshold. Data were entered into SPSS 18.0 databases and processed using its statistical functions, Student t-test, ANOVA F, Chi2 test, linear trend.

RESULTS AND DISCUSSION

The prevalence of sepsis with oral-maxillofacial portal of entry during the study period was bimodal, with a peak frequency in 2015 (35% of all cases) and in 2013 (22.5% of all cases).

The increasing trend in the incidence of this disease was due on the one hand to the improved techniques for causal agent identification and on the other hand to the involvement of an increasing number of risk factors.

During the study interval the disease was more common in men (70%), M/F ratio 2.3/1, mainly living in rural areas (62%). Age of patients included in the study ranged from 18 to 85 years, mean age 49.75 ± 18.15 years.

Chronic underlying disorders have a major impact on the outcome of patients with sepsis. Of the chronic diseases in the medical history of our patients we mention in order of their frequency: cardiovascular diseases (36.5%), obesity (45%), liver diseases (32%), malignancies (25%), kidney diseases (15%) and diabetes mellitus (10.5%).

Systemic infection was community-acquired in 120 (60%) of the study patients, being more common in women (58.3%; $p = 0.884$), mean age approximately 50 years ($p = 0.902$), and in rural patients (65%; $p = 0.833$). The remaining patients had hospital-onset sepsis.

In 38 cases (19%), the causal agent responsible for the disease was *S. aureus*, 1.5% being methicillin-resistant (MRSA) strains. Of the *Viridans* group of streptococci, the most frequently isolated was *Streptococcus salivarius* (15%) - 5% MDR strains, *Streptococcus mitis* (13%) - 2% MDR strains and *Streptococcus anginosus* (12%) - 2% MDR. β -hemolytic streptococcus was identified in 15.5% of cases. *Candida* sp and *Pseudomonas aeruginosa* were identified in 9% of patients. Anaerobic flora was positive for cocci/bacilli in 7% of subjects. Of the *S. epidermidis* strains (5.5% strains), 1% were MDR. Also identified were 6.5% positive *Acinetobacter* strains. Five percent of patients tested positive for *Klebsiella* and *E. coli*. The other causal agents were detected in low percentages (table1.).

Table I. Distribution of sepsis cases by causal agent

INVOLVED SPECIES	Susceptible		Resistant	
	No.	%	NR.	%
<i>S. aureus</i>	35	17.5	3	1.5
<i>S. epidermidis</i>	9	4.5	2	1.0
<i>Acinetobacter</i>	13	6.5		
<i>Pseudomonas aeruginosa</i>	15	9.0	3	1.5
Streptococ β hemolytic	28	14.0	3	1.5
<i>Streptococcus mutans</i>	16	8.0	5	2.5
<i>Streptococcus salivarius</i>	20	10.0	10	5.0
<i>Streptococcus mitis</i>	22	11.0	4	2.0
<i>Streptococcus anginosus</i>	20	10.0	4	2.0
<i>Klebsiella</i>	10	5.0	3	1.5
<i>Proteus</i>	3	1.5		
<i>E. coli</i>	10	5.0		
<i>Clostridium</i>	1	0.5		
<i>Candida</i> sp	18	9.0		
Anaerobic flora: cocci/bacili	14	7.0		

Most systemic infection with streptococci *mutans* (47.6%), *mitis* (42.3%) and *salivarius* (47.6%) were recorded in patients aged 40-59 years, while β -hemolytic streptococcus had a peak frequency in the age group 50-59 years (35.5%), but frequency distributions (table 2.) were not statistically significant ($p = 0.500$).

Table 2. Age-group distribution of sepsis cases according to the causal streptococcal species

Age group (years)	β hemolytic streptococcus		<i>Streptococcus mutans</i>		<i>Streptococcus salivarius</i>		<i>Streptococcus mitis</i>		<i>Streptococcus anginosus</i>	
	n	%	n	%	n	%	n	%	n	%
< 20	2	6.5	-	-	-		-	-	2	8.3
20-29	1	3.2	-	-	5	16.7	-	-	2	8.3
30-39	4	12.9	4	19.0	7	23.3	6	23.1	3	12.5
40-49	5	16.1	10	47.6	10	33.3	11	42.3	7	29.2
50-59	11	35.5	7	33.3	8	26.7	5	19.2	4	16.7
60-69	7	22.6	-	-	-	-	4	15.4	3	12.5
70-79	1	3.2	-	-	-	-	-	-	2	8.3
80-89	-	-	-	-	-	-	-	-	1	4.2

When analyzing the epidemiologic characteristics of patients according to the source of infection we found the following:

- male gender (43.8%; $p=0.884$), age over 50 years ($p = 0.902$), urban residence (37.5%; $p=0.883$) and antibiotic therapy (50%; $p=0.108$) were not statistically significantly correlated with nosocomial infection;

- previous hospitalizations (50%; $p=0.027$) and MDR (11.3%; $p=0.009$) were significantly more common in patients with nosocomial infections.

In the studied cases, *S. aureus* was sensitive to vancomycin (100%), imipenem (90%) and tobramycin (80%). (fig.1).

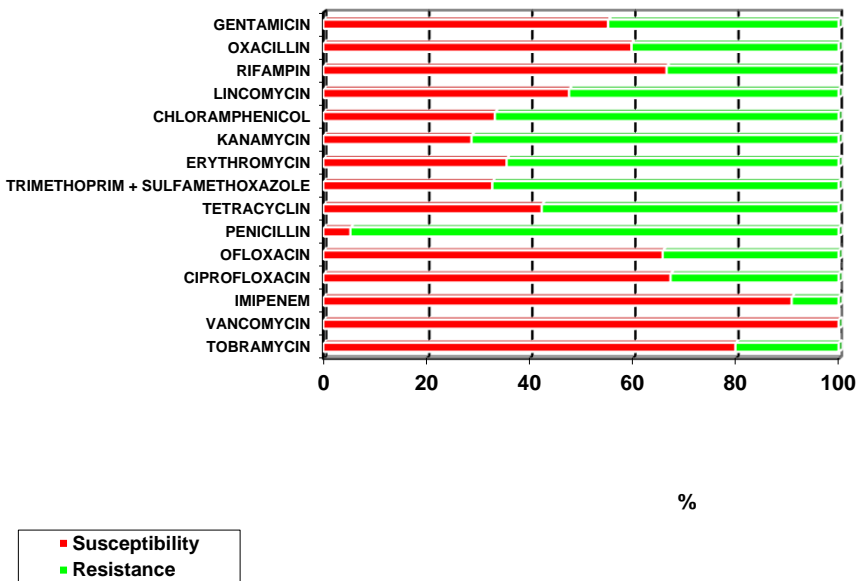


Fig. 1. Antibiotic susceptibility and resistance of *S. Aureus* strains

Antibiotic susceptibility of β -hemolytic staphylococcus strains isolated from patients diagnosed with sepsis showed: increased resistance to erythromycin (65%), gentamicin (63%); increased susceptibility to trimethoprim-sulfamethoxazole (90%); 100% susceptibility to vancomycin, teicoplanin, linezolid (Ifig. 2.).

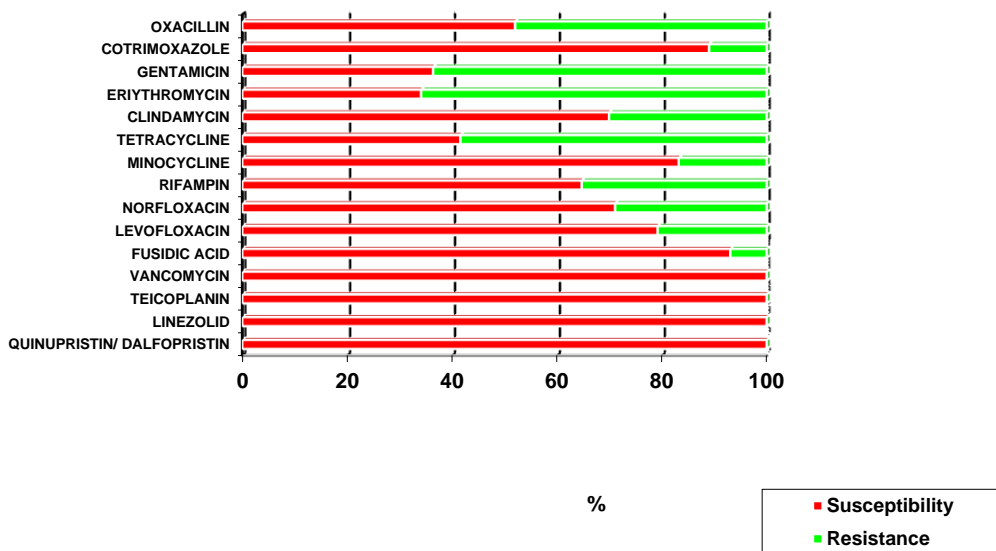


Fig. 2. Antibiotic susceptibility and resistance of β hemolytic staphylococcus strains

Cardiovascular involvement (organic and functional) was the most frequent site of secondary sepsis (36.5%), more common in men older than 50 years, and of staphylococcal etiology.

Facial skin involvement (organic and functional) was found in 33% of patients, most commonly women younger than 50 years, and of streptococcal etiology.

Liver involvement (organic and functional) was recorded in 32% of patients, most commonly men under 50 years of age, and of streptococcal etiology.

Sepsis-associated malignancies were identified in 25% of patients, most commonly in women younger than 50 years and of staphylococcal and streptococcal etiology.

Kidney involvement was present in 15% of patients, most commonly men over 50 years, and of staphylococcal etiology.

Ear involvement was detected in 10.5% of patients in the form of acute suppurative otitis media (20 patients) and unilateral sensorineural hearing loss with the contralateral ear possessing normal audiometric function (1 case). It was more common in women aged 50 years and was of streptococcal etiology.

Involvement of oral cavity was recorded in 16% of patients, most often in the form of lesions that extended beyond the confines of the floor of the mouth (7.5%) and maxillary sinusitis (5.5%). According to epidemiologic characteristics it was more common in women younger than 50 years and of streptococcal etiology.

Gingivitis and periodontitis patients were at significantly higher risk for sepsis (OR = 1.58, 95% CI = 1.14 to 2.19, $p = 0.01$), bacterial infections (OR = 2.15, 95% CI = 1.51 to 3.07; $p < 0.01$), fungal infections of the oral cavity (OR = 2.16; 95% CI = 1.43 to 3.28; $p < 0.01$) or other infectious complications (OR = 2.10; 95% CI = 1.63 to 2.84; $p < 0.01$).

Focal infections of oro-dental origin signify the fact that an oral focus of infection can act as the site of origin for dissemination of pathogenic organisms to distant body sites. This concept is controversial since it is difficult to prove the oral origin of germs responsible for an extra-oral infection (Persac S., et al., 2011).

In our prospective study, *S. aureus* was the main causal agent incriminated in the development of oral-dental sepsis.

According to the world literature, oral *Viridans* group streptococci are the species involved in the genesis of infective endocarditis and dental caries: *S. mutans*, *S. mitis*, *S. anginosus*, *S. sanguinus* and *S. salivarius* (<http://www.aae.org> / Colleagues).

Most of the study patients received antibiotic therapy prior to surgery (87.5%). It was found that antibiotic prophylaxis was not effective against the isolated pathogenic strains, particularly MRSA, enterococcus species and Gram-negative bacilli, additional prophylactic measures being required. MRSA was isolated in 45% of all periarticular infections.

CONCLUSIONS

Age under 50 years, male gender, urban residence, immunosuppression, recent medical history (previous hospitalization and antibiotic therapy) correlated significantly with the oral-maxillofacial involvement, which underlines the importance of outpatient follow-up of moderate and severe oral infections.

The insidious onset described in 54.6% of patients did not raise suspicion of a life-threatening condition such as sepsis.

A significantly higher percentage of patients with healthcare-associated infections developed MRSA sepsis than those with community-acquired infections, which is not a negligible percentage (38.5%).

The severe respiratory (43.1%) and the neuromeningeal manifestations (25.7%) were factors contributing to timely consultation with an infectious disease specialist.

Secondary involvement of the central nervous system (33.3%) was significantly more common in the immunosuppressed patients and in those with healthcare-associated infections and secondary cardiovascular involvement more frequent in patients with healthcare-associated infections.

In the patients with risk factors for methicillin resistance the first-line therapeutic options should be reconsidered: clindamycin, trimethoprim-sulfamethoxazole, new cyclins. The alternatives include vancomycin, teicoplanin and linezolid.

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