THERAPEUTIC STRATEGIES IN SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

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THERAPEUTIC STRATEGIES IN SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

DOCTORAL THESIS ABSTRACT

Scientific supervisors:

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PhD Candidate
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The doctoral thesis includes:

- Part I: Current stage of knowledge regarding the sepsis with oro-maxillary portal of entry, comprising 33 pages
- Part II: Personal contribution to the topic, organized in 4 chapters comprising 93 pages
- Bibliography comprising 304 bibliographic references
- Abbreviations
- The thesis contains 83 tables and 77 figures
- Articles published in IDB indexed journals: 2 first-author and 2 co-authored
- Articles published in ISI journals: 1 first-author, 3 co-authored, and 3 in printing.

Note: the abstract includes selective iconography and bibliography, but their numbering and content in the thesis are preserved.

Keywords: sepsis, oro-maxillofacial, multidrug resistant strains
THERAPEUTIC STRATEGIES IN SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

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CHAPTER 3
CHARACTERISTICS OF SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY IN PATIENTS IN NORTHEASTERN ROMANIA

Objectives
- to determine the incidence of sepsis with oro-maxillofacial portal of entry in the patients admitted to the Iași “Sf. Paraschiva” Infectious Diseases Hospital, referral center for all sepsis cases in Moldova region where case-appropriate therapy is decided;
- to comparatively determine the clinical-evolutive feature depending on the associated comorbidities, type of infection (community-acquired or nosocomial), access to medical care, presence of septic metastases, precocity of the etiologic diagnosis and initiation of appropriate therapy, so that the preventive measures to be adapted to the source of etiologic agent;
- to identify the pattern of susceptibility in the interval 2003-2012 in view of rethinking the empirical therapeutic regimens;
- to identify the most effective regimens (Carmeli score) and evaluate the prognostic factors in view of improving case management.

This retrospective study aimed at establishing the incidence of sepsis with orofacial portal of entry and studying the causal relationship between the disease and the incriminated risk factors (factors in the living environment, community, occupational environment, behavioral factors).
Material and method. Retrospective clinical trial conducted by analyzing the medical records of 130 patients admitted to the Iași Infectious Diseases Iasi in the interval 2003-2012; its aim was that based on the obtained results to draw relevant conclusions, intended to be helpful to clinicians in making a diagnosis of sepsis and monitoring its course.

Methodology included:
- data on exposure – identification and importance/impact of the risk factor using accepted, standardized methods;
- data on effect (health, morbidity, prognosis) – obtained through targeted medical examinations, and standardized and properly selected biomarkers.

The diagnosis of sepsis was made when at least two of the following four criteria were present within an infectious context:

- fever > 38°C or hypothermia < 36 °C;
- heart rate > 90 beats/minute;
- respiratory rate > 20 breaths/minute or PaCO₂ < 36 mmHg;
- white blood cell count > 12 000/mm³ or < 4000/mm³ or segmented neutrophils > 10%

In cases of severe sepsis, to the characteristic clinical picture is added one of the following symptoms associated to organ dysfunction (244):

- arterial hypoxemia (PaO₂/FiO₂ < 300 in intubated patients or PaO₂ < 60 mmHg in patients not receiving artificial ventilation);
- acute oliguria (urine output <0.5 ml/kg/hour or 45mmol/l for at least two hours);
- creatinine increase > 3.5mg/dL or > 0.5 mg/dl compared to the level recorded the previous day;
- metabolic acidosis (pH < 7.20 or lactic acid > 1.5 mmol l);
- coagulation abnormalities (International Normalized Ratio
(INR)> 1.5 or prothrombin time> 60 seconds) or thrombocytopenia (Tr/ platelet count <100 000 / mm³);
- ileus (absent bowel sounds) or hematemesis/melena (with no evidence of organic causes);
- Bilirubinemia (total bilirubin> 4 mg/dL or 70 mmol/L) and AST (aspartate aminotransferase)> 25-50 IU/L;
- acute encephalopathy with recently altered mental status (Glasgow scale <6 in the absence of sedation).

From epidemiological point of view, in recent years there is an increasing incidence of sepsis and higher sepsis rates among males and persons living in urban areas.

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

Various comorbidities were found in 82.3% of our patients. Of the personal medical history data, hypertension, toxic hepatopathies and renal failure had a major impact on the subsequent course of sepsis.

Causative agent distribution revealed statistically significant gender and age-group differences in the number of cases with S. aureus sepsis, female gender and age-group over 50 years being more commonly affected.

Patients with healthcare-associated infections developed methicillin-resistant staphylococcus aureus (MRSA) sepsis in a significantly higher proportion than those with community-acquired infections, percentage that cannot be overlooked (38.5%).

Using Carmeli score proved to be useful in identifying the source of infection (community-acquired or healthcare-associated) and in the initiation of first-line treatment.
Over 92% of the patients enrolled in the study were quantified as at high risk for infection with multidrug-resistant S. aureus strains (Carmeli score 2 and 3). Carmeli score 3 was significantly more commonly recorded among male patients. Age below 50 years, immunosuppression and MRSA strains were statistically significantly correlated with late hospital admission. Insidious onset described in the approximately 55% of patients did not raise the suspicion of a condition with high severity potential such as sepsis. Respiratory (43.1%) and neuromeningeal manifestations (25.7%), due to their clinical severity, were factors associated with the early decision to seek medical care from an infectious disease doctor. Secondary central nervous system involvement (33.3%) was significantly more frequent in immunosuppressed patients 1. with/2. and in those with healthcare-associated infections, requiring their careful monitoring to prevent these complications. Secondary cardiovascular involvement (20%) was significantly more frequent in patients with healthcare-associated infections, thus supporting the data in the literature on the importance of observing strict aseptic maneuvers and the guidelines for the prevention of infections associated with them. Beta-lactams remain a first-line treatment option in mild infections in patients without risk factors. In patients with risk factors for developing methicillin resistance, the first-line treatment options should be reconsidered and antibiotics such as clindamycin, trimethoprim-sulfamethoxazole, or new cyclins should be used. In hospital settings the alternatives include: vancomycin, teicoplanin and linezolid.

CHAPTER 4
RISK FACTORS FOR SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

Objectives. To determine the risk factors associated appropriate preventive measures, improving the quality of life of patients and reducing healthcare-related costs with sepsis with oro-maxillofacial portal of entry in view of initiating the most

Material and method. In order to achieve the objectives of this study a study group of consisting of 200 patients admitted to the Oro-Maxillofacial Surgery and ENT clinics of the Iasi "Sf. Spiridon" Emergency Hospital between 2010-2015 was created. From an epidemiological point of view, in recent years an increase in sepsis rate, predominance of male gender and of urban cases were found.

Fig. 4.1. Distribution of sepsis cases in the interval 2010-2015

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

Of the study patients 82.3% presented various comorbidities. Of the personal medical history data, hypertension, toxic hepatopathies and kidney failure had a major impact on the subsequent development of sepsis.

To assess the risk of infection with multidrug-resistant staphylococcus strains the Carmeli score was used, and based on it patients with multidrug-resistant strains were classified into three categories (Fig. 4.14):

- **Low risk** (Carmeli score 1 – community acquired infection) - 7 patients (63.6%);
- **Medium risk** (Carmel score 2 – healthcare-associated infections) - 1 patient (9.1%);
- **Severe risk** (Carmeli score 3 – nosocomial infection) - 3 patients (27.3%).

![Fig. 4.14. Case distribution according to Carmeli score](image-url)
A significantly higher proportion of patients with healthcare-associated infections developed methicillin-resistant staphylococcal sepsis compared to patients with community-acquired infections, percentage that cannot be overlooked (38.5%).

Table 4.VII. Epidemiological characteristics of patients according to infection source

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nosocomial (nr=80)</th>
<th>Community (nr=120)</th>
<th>p</th>
<th>RR</th>
<th>IC95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, no (%)</td>
<td>35 (43.8%)</td>
<td>50 (41.7%)</td>
<td>0.884</td>
<td>1.09</td>
<td>0.59-2.01</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>50.4±16.1</td>
<td>49.8±17.2</td>
<td>0.902</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urban residence, no (%)</td>
<td>30 (37.5%)</td>
<td>42 (35.0%)</td>
<td>0.833</td>
<td>1.11</td>
<td>0.59-2.09</td>
</tr>
<tr>
<td>Antibiotic therapy, no (%)</td>
<td>40 (50.0%)</td>
<td>45 (37.5%)</td>
<td>0.108</td>
<td>1.67</td>
<td>0.90-3.08</td>
</tr>
<tr>
<td>Previous admissions, no (%)</td>
<td>40 (50.0%)</td>
<td>40 (33.3%)</td>
<td>0.027</td>
<td>2.00</td>
<td>1.08-3.73</td>
</tr>
<tr>
<td>MDR, no (%)</td>
<td>9 (11.3%)</td>
<td>2 (1.7%)</td>
<td>0.009</td>
<td>7.48</td>
<td>1.45-51.6</td>
</tr>
</tbody>
</table>

Age below 50 years, immunosuppression and MRSA were significantly correlated with late admission.

Table 4.VI. Epidemiological characteristics of patients according to time of admission to hospital

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Long hospital stay (no=89)</th>
<th>Short hospital stay (no=111)</th>
<th>p</th>
<th>RR</th>
<th>IC95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, no (%)</td>
<td>55 (61.8%)</td>
<td>85 (76.6%)</td>
<td>0.035</td>
<td>0.49</td>
<td>0.26-1.00</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>47.30±15.0</td>
<td>57.08±15.2</td>
<td>0.020</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rural residence, no (%)</td>
<td>69 (77.5%)</td>
<td>55 (49.5%)</td>
<td>0.001</td>
<td>3.51</td>
<td>1.81-6.87</td>
</tr>
<tr>
<td>Immunosuppression, no (%)</td>
<td>39 (43.8%)</td>
<td>25 (22.5%)</td>
<td>0.002</td>
<td>2.68</td>
<td>1.39-5.18</td>
</tr>
<tr>
<td>Nosocomial infections, no (%)</td>
<td>32 (36.0%)</td>
<td>38 (34.2%)</td>
<td>0.917</td>
<td>1.08</td>
<td>0.58-2.02</td>
</tr>
<tr>
<td>MDR, no (%)</td>
<td>9 (10.1%)</td>
<td>2 (1.8%)</td>
<td>0.024</td>
<td>6.13</td>
<td>1.19-42.31</td>
</tr>
</tbody>
</table>
The insidious onset described in 54.6% of patients did not raise the suspicion of a potentially life-threatening disease, such as sepsis. The intensity of respiratory (43.1%) and neuromeningeal manifestations (25.7%) was a factor associated with early seeking medical care. Secondary central nervous system involvement (33.3%) was significantly more frequent in immunosuppressed patients with and in those with healthcare-associated infections. Secondary cardiovascular involvement (20%) was significantly more frequent in patients with healthcare-associated infections. Beta-lactams remain a first-line treatment option in mild infections in patients without risk factors. Resistance to third-generation cephalosporins and aztreonam progressively increased in Romania after their introduction in therapy. Within 10 years, the percentage of isolates resistant to ceftazidime has doubled. The tested *S. aureus* strains high MIC 90 values (64µg/ml) for tetracycline and kanamycin and high-level resistance to kanamycin, erythromycin, trimethoprim-sulfamethoxazole, for penicillin the resistance rate being 94.7%.
Susceptible Intermediate Resistant

Fig. 4.21. Antibiotic susceptibility and resistance of *S. aureus* strains

CHAPTER 5
QUALITY OF LIFE IN PATIENTS WITH SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

The aim of this study was to comparatively analyze the impact of the diagnosis of sepsis with oro-maxillofacial portal of entry on oral health and quality of life according to gender, age and area of residence.

**Material and method.** Observational study was conducted in a sample of 50 patients admitted to the Oro-Maxillofacial Surgery Clinic of the Iasi "Sf. Spiridon" Emergency Hospital during 2015-
2016. Inclusion criteria were: age over 18 years; firm diagnosis confirmed by the fact that all clinical and laboratory (bacteriological investigations, hematological, biochemical and imaging) criteria are met. The OHIP (Oral Health Impact Problems/Profile) questionnaire was used for assessing the global self-reported oral health status (OHRQoL) using seven domains: Functional limitations, Physical pain, Psychological discomfort, Physical Disabilities, Psychological disability, Social disabilities and handicap. Principle: the same questionnaire is applied to all cases and a primary score is calculated for each respondent; the standardized score scale ranges from 0 to 70, a low score reflecting a "better" global oral health status (248).

**Results.** The quality of life score ranged from 6 to 57, a medium score reflecting a moderately impaired quality of life (medium score 40.06 out of a maximum of 70) (table 5.XII). Depending on sociodemographic characteristics the following were noted (Fig. 5.8):

- no significant gender differences (39.80 vs. 40.32; \( p = 0.885 \));
- a significantly higher medium score was recorded in the 40-49 years age-group (47.23; \( p = 0.012 \));
- no statistically significant differences in terms of area of residence (40.41 vs. 39.65; \( p = 0.834 \)).

**Table 5.XII. Descriptive indicators of quality of life score according to sociodemographic characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>95% Confidence Interval</th>
<th>Min</th>
<th>Max</th>
<th>( p ) for F_Aanova test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases</td>
<td>50</td>
<td>40.06</td>
<td>12.49</td>
<td>1.77</td>
<td>36.51 - 43.61</td>
<td>6</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>39.80</td>
<td>12.51</td>
<td>2.50</td>
<td>34.64 - 44.96</td>
<td>8</td>
<td>55</td>
<td>0.885</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>40.32</td>
<td>12.71</td>
<td>2.54</td>
<td>35.07 - 45.57</td>
<td>6</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>
THERAPEUTIC STRATEGIES IN SEPSIS WITH ORO-MAXILLOFACIAL PORTAL OF ENTRY

<table>
<thead>
<tr>
<th>Age-groups</th>
<th>20-29 years</th>
<th>30-39 years</th>
<th>40-49 years</th>
<th>50-59 years</th>
<th>60-69 years</th>
<th>Area of residence</th>
<th>Urban</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>11</td>
<td>13</td>
<td>14</td>
<td>7</td>
<td></td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>20-29 years</td>
<td>27.00</td>
<td>43.00</td>
<td>47.23</td>
<td>38.43</td>
<td>34.71</td>
<td>Urban</td>
<td>40.41</td>
<td>39.65</td>
</tr>
<tr>
<td>30-39 years</td>
<td>18.28</td>
<td>8.59</td>
<td>8.64</td>
<td>11.99</td>
<td>12.55</td>
<td>Rural</td>
<td>13.25</td>
<td>11.81</td>
</tr>
<tr>
<td>40-49 years</td>
<td>8.17</td>
<td>2.59</td>
<td>2.40</td>
<td>3.20</td>
<td>4.74</td>
<td></td>
<td>2.55</td>
<td>2.46</td>
</tr>
<tr>
<td>50-59 years</td>
<td>4.31</td>
<td>37.23</td>
<td>42.01</td>
<td>31.50</td>
<td>23.10</td>
<td></td>
<td>35.17</td>
<td>34.55</td>
</tr>
<tr>
<td>60-69 years</td>
<td>49.69</td>
<td>48.77</td>
<td>52.45</td>
<td>45.35</td>
<td>46.32</td>
<td></td>
<td>45.65</td>
<td>44.76</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>28</td>
<td>28</td>
<td>13</td>
<td>9</td>
<td></td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>53</td>
<td>57</td>
<td>53</td>
<td>47</td>
<td></td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

Fig. 5.8. Mean quality of life score (OHRQoL) depending on sociodemographic characteristic

An observational study on the impacts of oral disorders in 3033 subjects interviewed over the phone in 2009 by David Locker, concluded that 1 in 5 Canadian adults (20%) reported experiencing functional limitation and psychosocial impact/disability (171). In a 2010 study, Cohen-Carneiro et al. found that the impact of oral cavity problems was greater in people living in periurban areas than in urban areas and in women compared to men (Cronbach alpha = 0.89). OHIP-14 questionnaire applied to these subjects was adapted to rural population in the Amazon states (64)
**Conclusions.** Age-group 40-49 was the most affected, a significantly higher median OHRQoL score being recorded in these patients. Distribution by gender and area of residence showed no significant differences in quality of life.

Of the patients experiencing pain, 56.4% reported social disabilities, 41.9% psychological disabilities and 35.6% physical disabilities, results that can be extrapolated to the general population. Handicap was associated with psychological disabilities (43.8%), physical disabilities (40.3%) and social disabilities (33.2%). The presented data illustrate the negative impact of oromaxillofacial manifestation on quality of life, requiring follow-up programs of the patients with such disorders, so that, through individualized treatment plans, the patients and their families to overcome the problems. The version of OHIP-14 questionnaire used in this study proved to be a valid and useful instrument for assessing the quality of life in patients with oro-dental sepsis.

**CHAPTER 6**

**FINAL CONCLUSIONS**

1. The oral cavity is a portal of entry and an important site of microbial infections that affect the general health status.
2. Many systemic diseases have oral manifestations, these being a first sign of damage to other organs.
3. All data in the medical literature have demonstrated that oromaxillofacial sepsis doubles the risk of bacteremia. To reduce oral infections and their systemic complications, maintaining optimal oral health is vital.
4. The etiological spectrum of potentially severe infections has expanded considerably in recent years due to inadvertent
administration of antibiotic therapy, the widespread use of invasive medical maneuvers improvement of techniques for the identification of infectious pathogens, increased life expectancy, and immunosenesence. Of the commonly involved pathogens, Gram-positive bacteria (especially staphylococci) rank first, followed by fermenting (E. coli, P. aeruginosa, Proteus) or nonfermenting Gram negative bacilli (Acinetobacter) and fungi (represented mainly by Candida species).

5. Patients with compromised immune system and hospitalized patients are at higher risk of morbidity due oro-maxillofacial infections.

6. Studies on animals and humans have shown an association between periodontal diseases and diabetes mellitus, cardiovascular diseases, stroke and adverse pregnancy outcomes.

7. The literature has shown that different staphylococcal species were frequently isolated in the oral microflora in both healthy or sick children and adults. Further studies are needed to determine whether the presence of staphylococci is transient or not. This implies that the oral cavity can be considered a possible source of infection at distant sites, when other sources of infection have been ruled out.

Unele studii au evidențiat că tehnicile genomice și proteomice au luat serios în calcul rolul unor vaccinuri în combaterea biofilmului produs de S. aureus.

8. S. aureus is the most common etiologic agent in acute infections, and its ability to form biofilms leads to chronic diseases. Current therapies for the treatment and prevention of biofilm formation are limited to surgery and long-term antibiotic treatment.

9. Some studies have shown that genomic and proteomic techniques have taken seriously into account the role of some vaccines in the eradication of S. aureus biofilm infections.
10. The immune mechanisms of carriers of *S. aureus* with oro-maxillofacial portal of entry must be thoroughly investigated, and in non-carriers, prophylaxis of *S. aureus* infection requires special attention.
11. The favorable course of the disease depended on the precocity of etiologic diagnosis and initiation of appropriate therapy.
12. Oral cavity and its functions may be affected by various drug therapies.
13. Early aggressive treatment increases the chances of surviving sepsis. Patients with severe sepsis should be monitored carefully and treated in intensive care unit.
14. In patients with risk factors for methicillin resistance, the first-line treatment options should be reconsidered and the following antibiotics should be used: clindamycin, trimethoprim-sulfametoxaxol, or new cyclins. In hospital settings, the alternatives include vancomycin, teicoplanin and linezolid.
15. The presented data illustrate the negative impact of oral-maxillofacial manifestations on quality of life, which requires follow-up programs of the patients with these disorders, so that, through individualized treatment plans, the patients and their families to overcome the health-related problems.

**ORIGINALITY OF THE THESIS, ITS CONTRIBUTION TO KNOWLEDGE AND IMPLICATION FOR RESEARCH AND PRACTICE**

The thesis deals with one of the topics of major concern and widely debated in the international literature on systemic microbial infections, a topic of interest in clinical and preventive medicine, namely sepsis with oro-maxillofacial portal of entry.

The research topic is of major importance for our country, where scientific research is mainly focused on the study of nosocomial infections and not on the quality of life of the hospitalized patient.
Identification and isolation of patients at risk, the application of new decontamination regimens, use of new chemotherapy drugs or restriction of selected classes of antibiotics appear to be promising strategies for limiting transmission of the pathogenic staphylococcus strains increase survival and reduce hospital costs. The quality of life of patients with oro-dental sepsis may not be well understood and properly evaluated without relying on the measurement of patients' self-perceptions and self-assessments and without measuring the positive aspects in their lives.

The results of the diagnostic screening of sepsis patients, analysis of the etiological spectrum of this condition and of the associated comorbidities as well as the study of the mechanisms of antibiotic resistance to circulating strains could be used in a national program for the follow-up of patients at high risk of developing sepsis, this way benefiting from/providing positive feedback on the outcome of these cases.

LIST OF ARTICLES ON THE RESEARCH TOPIC PUBLISHED DURING PhD STUDIES

Articles published in ISI journals


Source:

Articles published in IDB indexed journals:


**Articles that are going to be published (ISI):**


of Computational and Theoretical Nanoscience, USA, impact factor 1,666 (2015).


Article that is going to be published (BDI):

BIBLIOGRAFIE SELECTIVA


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