Septicaemia is a severe and debilitating clinical condition that substantially alters the lives of those afflicted; this is a potentially life-threatening medical condition that's associated with an infection. The infection's signs and symptoms must fulfill a minimum of two criteria of a Systemic Inflammatory Response Syndrome (SIRS). Severe sepsis (defined as a sepsis case associated with organ dysfunction), is associated with a high mortality rate and is caused by an infection induced immune response and as a result it has a major impact on healthcare expenditure and resources [1].

The worldwide incidence of septicaemia is estimated to rise up to 18 million new cases per year, but the real morbidity rates of sepsis are underestimated [2]. Within European Union (EU), the incidence of sepsis has been estimated at 90.4 new cases per 100,000 inhabitants. In Great Britain, Intensive Care National Audit and Research Centre (ICNARC) data (which identifies cases occurring in hospital settings, with typical bed costs/day of around £70), estimates 150,000 new cases of sepsis and around 44,000 associated deaths per year (in 2015) [3]. Treatment for sepsis often involves a prolonged stay in the intensive care unit and complex therapies, which incur high costs. Around 70% of patients with sepsis are managed in critical care hospital settings, with typical bed costs/day of around £2000, this equates to direct costs of over £2.5 billion per year. The Great Britain Sepsis Trust has estimated that a typical medium-sized general hospital could save £1.25 million per year through improved management of sepsis and that achieving 80% delivery of the basic standards of care is likely to save 10,000 lives per year and around £170 million annually for the National Health System [4].

Septicemia with its associated complications remains a major economic burden in the world [1]. The Agency for Healthcare Research and Quality lists septicaemia as the most expensive condition treated in United States hospitals; sepsis is the single most expensive reason for hospitalization at the moment, costing more than $20 billion (in 2011), increasing on average annually by 11.9% [4]. Atlanta Center for Disease Control and Prevention has been estimated that if the United States as a whole achieved earlier sepsis identification and evidenced based treatment, there would be 92,000 fewer deaths annually, 1.25 million fewer hospital days annually and reductions in hospital expenditures of over $1.5 billion.

In Romania, the number of new cases of sepsis (8079 in 2009) and deceases caused by it registers a more increased growth rate than the regional and global average [5]. Public health specialists have said that the increasing trend in the incidence of sepsis 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 (including increased awareness and tracking of the condition, an aging population, the increased longevity of people with chronic diseases, the spread of antibiotic-resistant organisms, an upsurge in invasive procedures and broader use of immunosuppressive and chemotherapeutic agents) [6].

Sepsis, which has a dental or oral-maxillofacial entrance gate of the pathogen agent, became in the last decade, an important public health issue in dental medicine due to the increasing prevalence rate of this pathology, high rate of fatality, adverse prognosis and high costs for diagnosis and treatment [6].

Oral infections have become an increasingly common risk-factor for sepsis and systemic diseases, which clinicians should take into account. The relationship between oral and general health has been increasingly acknowledged during the past two decades [7].

Many public health studies, including a number of meta-analyses and systematic reviews, have linked poor oral health with various systemic diseases: cardiovascular disease, diabetes and metabolic syndrome, endocarditis, cancer and kidney disease [7]. Oral health problems and health conditions like obesity or diabetes may be the result of a mouth infection, but they may also lead to an increased risk of other infections. A recent study showed that tooth loss is significantly associated with an elevated risk of cardiovascular disease [8].

The prognosis for patients with sepsis is dependent on the early establishment of the proper diagnosis and the quick initiation of antibiotic therapy [1]. Early identification and treatment of sepsis will have tremendous economic benefits, totally apart from saving lives and reducing the negative impacts of sepsis.

Recently, special attention has been given to new biomarkers associated with sepsis. Biomarkers are molecules that are correlated with disease states or states of altered physiology and may be used for early diagnose of the disease and for direct therapies [9].

In patients with sepsis, electrolyte abnormalities should be considered in the context of water balance. Hydro-electrolyte balance is one of the key issues in maintaining homeostasis in the body and it also plays important roles in protecting cellular function, tissue perfusion and acid-base status in patients with sepsis that have a dental or oral-maxillofacial as entrance gate of the pathogen agent [10].

The key to winning the campaign to combat sepsis is improved understanding of the epidemiology, pathogenesis of sepsis and discovery of novel therapies.

**Experimental part**

**Material and method**

The present retrospective study was conducted on 768 cases of sepsis registered in 2006-2016 period. Out of 127 (16.53%) cases with oral-maxillofacial and dental sepsis, 82 (10.68%) cases, that show a dental or oral-maxillofacial condition as entrance gate of the pathogen agent, was chosen as a representative group for the area of Moldavia, Romania. Out of the reported cases, there have been considered for study only those new cases of illness, for which the diagnosis was established.

It can be noticed that the dental entrance gate of the pathogen agent is rather frequent and most of the times neglected in the diagnosis of sepsis.

The aim of the study was to monitor the serum hydro-electrolyte disturbances and acid-base status in patients with oral-maxillofacial and dental sepsis. The main objective was to find the occurrence of disturbances among the different grades of sepsis and assess the type of dysfunction encountered.

Inclusion criteria were: patients over 18 years of age with sepsis diagnosis confirmed by positive findings on clinical exam, laboratory tests (biochemical, bacteriologic, hematologic) and imaging. Suspected or proven infection was associated with SIRS and sepsis diagnosed by the presence of organ dysfunction (as renal, respiratory, cardiac failure, neurologic impairment, disseminated intravascular coagulation or shock). The link between dental or oral-maxillofacial disease as entrance gate of the pathogen agent and sepsis was historically documented.

Patients who received antibiotics treatment in the last 14 days were thus excluded.

Ethical clearance for the study was obtained from the institutional ethical committee.

The strains were isolated from different biological or pathological products: blood, pus or seeding on catheters.

Biochemical laboratory examinations have a fundamental role in sepsis. Standard pre-investigative protocol was followed for the collection of biological products (no consumption of food and no smoking before blood collection) [11]. Blood was collected by venepuncture in first 12 hours of hospitalization [12] and samples were analyzed in an accredited medical laboratory.

For monitoring the electrolytes disturbances, the serum levels of sodium, potassium and chloride were dosed. The sodium and potassium were measured using a standardized chemistry analyzer for electrolyte levels (an ion-selective electrode analyzer) [13]. The alkaline reserve and the arterial pH changes were used for monitoring the acid-base status.

A database was generated using Microsoft Excel 2010 for Windows and the SPSS statistical software package (version 18.2 for Windows; SPSS, Inc., Chicago, IL, USA) was used in order to perform the statistical processing of data and statistical analysis [13, 14].

Biochemical serum levels of main electrolytes (Na+, K+ and Cl-) and acid-base status (pH and alkali reserve) have been expressed as mean ± S.D. [14]; there were used the “t” Student test, in order to check the statistical significance (SS) of the noticed differences.

The following indicators were calculated: prevalence (%), Odds Ratio (OR - relatively estimated risk) with its confidence interval (CI 95%) and attributable risk (AP). Also, we used the Pearson χ² test; the statistical significance was considered at p value less than 0.05. The interdependency between the studied variables and the intensity of the correlation was highlighted by the Pearson coefficient of correlation (r) [13].

**Results and discussions**

Considering the 127 cases of our study, 82 cases (64.57%) were cases of sepsis that have a dental or oral-maxillofacial entrance gate of the pathogen agent (infections with oral-dental origin showcase the fact that an oral focus of infection can act as the site of origin for dissemination of germs to distant body sites [7, 15]); this is controversial since it is difficult to prove the oral origin of germs responsible for an extra-oral infection [16].

In 71 (68.58%) cases the blood cultures were positive, whereas for the rest of the cases the pathogen agent was revealed in seeding on catheters (4.88%) or pus (8.54%).

**General caracteristics of patients**

The mean age of patients was 45.21 ± 21.57 years (CI 95%; 40.39-49.73).

In the present study it was found that the disease was more common in male subjects (55.91%); M/F ratio = 1.27/1. Most of the patients, 51 (62.20%), came from the rural area and only 31 (37.80%) from the urban area. Male gender, recent medical history (previous hospitalization and antibiotic therapy) and rural area were significantly correlated (χ² calculated = 8.17 > χ² table = 3.84, p<0.05, SS) with the dental and oral-maxillofacial involvement, which draws attention on the outpatient follow-up of moderate and severe oral infections. The explanation can be related...
to the fact that patients from the rural area have a decreased standard of living, limited access to specialized medical services and a precarious dental health [17].

The period of hospitalization varied between 1 and 38 days, a mean period of hospitalization being 14.07 ± 8.54 days (CI 95%: 13.12-16.38).

Patients with sepsis frequently have underlying comorbidities which predispose them to infections and may have an additive contribution to increase the fatality rate. Out of the chronic diseases reported in the medical history of our patients we mention the following, in order of their frequency: cardiovascular diseases (29.27%), diabetes mellitus (21.95%), kidney diseases (19.51%), haematological (14.63%), respiratory (8.54%), liver diseases (4.88%), obesity (3.66%), chronic alcoholism (3.66%), malignancies (2.44%) and ENT diseases (2.44%).

From 82 sepsis cases that have a dental or oral-maxillofacial entrance gate of the pathogen agent, the oral-maxillofacial involvement was recorded in 31 (24.14%) of them (OR = 3.22, CI 95%: 1.81 - 5.71, p value <0.05, \( \text{AP}=0.6899 \)):

- maxillary sinusitis of dental origin- 3 (9.68%) cases;
- mumps/parotid space abscess- 2 (6.45%) cases;
- suppuration of submandibular gland- 3 (9.68%) cases;
- surgery/ fractures- 6 (19.35%) cases; soft tissue injuries / cellulitis- 5 (16.13%) cases;
- plgemon of the mouth floor- 4 (12.90%) cases; multiple traumatic lesions 4- (12.90%) cases;
- implanted such as central venous catheter- 2 (6.45%) cases; mandibular osteitis and neoplasms of the palate- 1 (3.22%) case.

Dental involvement was recorded in 37 (29.13%) cases: dental infections (post-extraction alveolitis, endodontic foci) in 17 (45.95%) of the cases (OR = 0.97, CI 95%: 0.44-2.11, \( p <0.05 \)), out of which 4 (10.81%) having infective endocarditis; chronic/ acute periodontitis (serous or suppurated) in 21 (56.76%) of the cases (OR = 0.63, CI 95%: 0.29-1.37, \( p < 0.001 \)) and fungal infections of the oral cavity in 9 (24.32%) of the cases (OR = 2.56, CI 95%: 1.06 - 6.09, p value <0.05, \( \text{AP}=0.6093 \)). Other infectious complications were recorded in 33 (25.98%) cases (OR = 1.22, CI 95%: 0.66 - 2.27, \( p <0.05 \), \( \text{AP}=0.1803 \)).

The Carmeli score was used to assess the risk of infection. The cases were stratified into the following risk groups: low risk (Carmeli score 1 - community-acquired sepsis), 63 (76.83%) cases; medium risk (Carmeli score 2 - healthcare-associated sepsis), 17 (20.73% cases and severe risk (Carmeli score 3 - nosocomial sepsis), 2 (2.44%) cases.

In our study, the fatality rate was 29.27% (24 deaths). The main causal agent incriminated in the development of oral-dental sepsis in deceased patients was: anaerobic Gram-negative bacilli (20.83%), S. aureus (12.50%), methicillin-resistant Staphylococcus + Enterococcus spp. (4.16%), Acinetobacter Baumannii (8.33%), Proteus spp. (8.33%), oral Vindians group streptococci (in 16.67% of cases they are involved in the genesis of infective endocarditis), normal oropharyngeal flora (12.50%) and E. Coli (41.67%).

The severity of sepsis was frequently underdiagnosed [18].

Biochemical levels of sodium, potassium and chloride in serum

Electrolyte modifications were evaluated in the group of patients taken in the study, with the help of sodium, chloride, and potassium level assay, the results being synthetically presented in table 1.

The prevalence of electrolytes disturbances was: 15.85% for sodium, 69.15% for potassium and 55.50% for chloride. The most important and prevailing electrolyte imbalances are hypo- and hyper-states of sodium, potassium and chloride.

Sodium is the most abundant extracellular cation in the human body. Sodium determines serum osmolality which regulates water flow, as water moves from extra- to intracellular compartment until homeostasis is achieved [19]. Disturbances in serum sodium concentrations are a common clinical problem in patients with oral-maxillofacial and dental sepsis. Sodium imbalances are particularly important in patients who need intensive care because dysnatremia (both hypo- and hypernatremia) is significantly associated with poor prognosis and the increase of fatality rate in patients with sepsis [20].

After measuring the level of serum sodium in patients with sepsis in the studied group, the following were noticed: the mean value of sodium in the group of patients who survived was 131.94 mEq/l; normal natremia (139.14 ± 1.78 mEq/l) registered prevalence was 84.15% (69 cases); hypernatremia was registered in 6 (7.32%) cases, 2 (2.44%) of them, who had severe hypernatremia (over 150 mEq/l), deceased (OR=0.87, CI 95%: 0.16-4.61, \( p <0.05 \)); hyponatremia (under 133 mEq/l) was registered in 5 (6.10%) cases, out of which in 3 (3.65%) cases with severe hyponatremia (under 110 mEq/l) deceases occured (OR=0.45, CI 95%: 0.10-2.06, \( p <0.05 \)).

Symptoms of hyponatremia (headache, lethargy, nausea, disorientation, depressed reflexes) occur with a rapid decrease of serum sodium to < 125 mEq/l, and coma results from rapid decrease of serum sodium to < 110 mEq/l. The most dreaded complication in a patient with symptomatic hyponatremia is acute cerebral edema. Detection and treatment of hypernatremia requires recognition of non-specific symptoms (lethargy, irritability, thirst, hyperreflexia), identification of the underlying defects of water metabolism, correction of volume disturbances, and correction of hyperoncoticity. The most serious symptoms in patients with hypernatremia are due to osmolality changes in the central nervous system [19, 25].

Potassium is the most abundant intracellular cation in the human body, approximately 98% of the total potassium amount was found intracellularly.

Measuring the serum potassium level in the studied

### Table 1

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Sodium (Na⁺) (mEq/l)</th>
<th>Potassium (K⁺) (mEq/l)</th>
<th>Chloride (Cl⁻) (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>131.94</td>
<td>3.665</td>
<td>100.89</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>≈ 13.78</td>
<td>≈ 1.089</td>
<td>≈ 7.09</td>
</tr>
<tr>
<td>Minimum value</td>
<td>28</td>
<td>1.2</td>
<td>86</td>
</tr>
<tr>
<td>Maximum value</td>
<td>161</td>
<td>6.3</td>
<td>127</td>
</tr>
<tr>
<td>Confidence Interval 95% (CI 95%)</td>
<td>128.37-135.18</td>
<td>3.436-3.892</td>
<td>99.15-102.65</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>10.44</td>
<td>29.69</td>
<td>7.03</td>
</tr>
<tr>
<td>N (no. of cases)</td>
<td>82</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>Normal values</td>
<td>133-145</td>
<td>3.5-5.6</td>
<td>96.106</td>
</tr>
</tbody>
</table>

**CAPTIONS:**

- Sodium (Na⁺)
- Potassium (K⁺)
- Chloride (Cl⁻)

**Note:** Table 1 CHANGES OF SERUM ELECTROLYTE LEVELS IN STUDIED PATIENTS
A lot of medicines used in the intensive care units can also cause hyperkalemia (beta-blockers, inhibitors of renin-angiotensin-aldosterone system, potassium-sparing diuretics, heparin and its derivatives, trimethoprim, and non-steroidal anti-inflammatory drugs) [19]. Medications prescribed in the ICU are associated with hypokalemia because they drive extracellular potassium into cells [20].

The changes in EKG were studied in the cases found with hypokalemia, in order to evaluate the impact of changes in potassium. These are useful for quantifying potassium hypokalemia, in order to evaluate the impact of changes in potassium. Hypokalemia is often associated with hypokalemia (sympathomimetics, methylxanthines and dobutamine, insulin) because they drive extracellular potassium into cells [20].

The correlation between the pH value and the serum potassium value was evaluated for the entire studied group. The Pearson coefficient of correlation calculated value was r = 0.37, thus revealing a weak to moderate correlation, at p < 0.05. For the group of patients with sepsis who survived, the Pearson coefficient was r = 0.43 (moderate correlation) and r = 0.40 in the group of the 24 deceased, at the statistical significance threshold p < 0.05.

The value of serum potassium did not influence the fatality rate, but associating it with acidosis signals the gravity of the disease and the increase of death risk [21].

Table 2

<table>
<thead>
<tr>
<th>Indicators</th>
<th>pH</th>
<th>Alkali reserve (HCO3⁻) (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.468</td>
<td>22.51</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>± 0.103</td>
<td>± 5.31</td>
</tr>
<tr>
<td>Minimum value</td>
<td>7.28</td>
<td>9.0</td>
</tr>
<tr>
<td>Maximum value</td>
<td>7.69</td>
<td>41.0</td>
</tr>
<tr>
<td>Confidence Interval 95% (CI 95%)</td>
<td>7.418-7.513</td>
<td>20.13-23.94</td>
</tr>
<tr>
<td>Coefficient of variation %</td>
<td>1.38</td>
<td>23.59</td>
</tr>
<tr>
<td>N (no. of cases)</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>Normal values</td>
<td>7.36-7.44</td>
<td>22-26</td>
</tr>
</tbody>
</table>

The correlation between the pH value and the serum potassium value was evaluated for the entire studied group. The Pearson coefficient of correlation calculated value was r = 0.37, thus revealing a weak to moderate correlation, at p < 0.05. For the group of patients with sepsis who survived, the Pearson coefficient was r = 0.43 (moderate correlation) and r = 0.40 in the group of the 24 deceased, at the statistical significance threshold p < 0.05.

The value of serum potassium did not influence the fatality rate, but associating it with acidosis signals the gravity of the disease and the increase of death risk [21].

Measuring serum chloremia revealed the following results: mean chloremia in patients with sepsis who survived was 100.89 mEq/L and 112.71 mEq/L in the group of the deceased patients; normal chloremia had a prevalence of 44.44% (32 cases); hyperchloremia (over 106 mEq/L), which determines the emergence of hyperchloremic metabolic acidosis, was present in 19 (26.39%) cases, 2 (2.44%) of them being registered with severe hyperchloremia, in the case of which the patients died afterwards (OR = 3.05, CI 95%: 0.64-14.14; p value < 0.05, AP = 0.6721).

Hyperchloremia can be iatrogenic as a result of administering sodium chloride (0.9%) in order to maintain a normal sodemia. Hyperchloremic metabolic acidosis is due to the replacement of bicarbonate with chloride ions, in order to maintain plasma electroneutrality [20]. Metabolic alkalosis is frequently associated with hypopotassemia. Aldosteron activates potassium release in exchange for sodium (which is renally reabsorbed) at the apical pole of the epithelial cell at the level of the nephron distal convoluted tube. The reabsorption of sodium in exchange with H⁺ or K⁺ depending on the arterial pH value takes place at the level of the base pole [22].

**Serum levels of pH and alkali reserve**

The acid-base imbalance was evaluated in patients of the study group using the alterations of the pH value and alkali reserve, the results being presented in table 2.

The value of the serum pH normally varies between 7.36-7.44 (pH lower than 6.8 or higher than 7.8 is usually fatal). It is considered to be an acidosis when the pH registers values under 7.36, whereas in the case of alkalosis, the pH value is over 7.44.

As a result of measuring pH in the studied group of patients, the following can be noticed: the mean pH value of the patients who survived was 7.468; normal pH (7.36-7.44) had a prevalence of 34.48% (10 cases); acidosis, an important change in the acid-base balance, occurred in 6 (20.69%) cases; this may be caused either by the increase in partial pressure of the carbon dioxide in arterial blood (respiratory acidosis), either due to an increase in the concentration of organic or anorganic acids (metabolic acidosis) [23].

Total carbon dioxide is made up from CO₂, found as such in solution or bound by proteins, HCO₃⁻, CO₃²⁻ and H₂CO₃. In practice, ~90% out of the total CO₂ is represented by bicarbonate (HCO₃⁻). Bicarbonate represents the second plasmatic anionic fraction, its concentration being an important indicator of electrolyte distribution and anion deficit. Together with determining the pH in blood, the measuring of bicarbonate is useful in the diagnosis of sepsis, accompanied by the disturbance of acid-base balance [23]. Frequently enough, an abnormal HCO₃⁻ value indicates a metabolic disturbance rather than a respiratory one; thus, the decrease of HCO₃⁻ emphasizes a metabolic acidosis and an increase of HCO₃⁻ indicates metabolic alkalosis [24].

Monitoring alkali reserve (HCO₃⁻) in the studied group revealed the following aspects: the mean value in patients
with sepsis who survived was 22.51 mEq/L; normal alkali reserve (22-26 mEq/L) had a prevalence of 24.14% (21 cases), out of the 13 (16.05%) cases with values over 25 mEq/L, there were registered moderately increased values (26-27 mEq/L) in 4 cases (4.94%) with multiple organ dysfunction; and 9 (11.11%) patients having hepato-renal dysfunction registered high values (28-30 mEq/L), 4 (4.94%) of them died afterwards (OR = 1.82, CI 95%: 0.45-7.31, p = 0.039, AP = 0.4505); in 47 (58.02%) cases there were registered moderately low values (under 21 mEq/L), 8 (9.88%) of these cases having severely decreased values (under 18 mEq/L), and 3 of them died (OR = 1.43, CI 95%: 0.34 - 5.99, p = 0.013, AP = 0.3006).

As the metabolic acidosis is characterized by the decrease of arterial pH under 7.35 as a result of primary decrease of bicarbonate (HCO3) concentration under 21 mEq/L, the correlation between arterial pH and bicarbonate was therefore evaluated. Thus, it was found that there is a slight to moderate correlation between their values, Pearson coefficient of correlation being r = 0.41, at p < 0.05. For the group of patients who survived, there was a moderate correlation between the 2 values with a Pearson coefficient of r = 0.44. In the group of the deceased patients, the Pearson coefficient values were r = 0.37 at p < 0.05 statistical significance threshold.

Patients with sepsis that have a dental or oral-maxillofacial disease as entrance gate of the pathogen agent experienced fluid imbalances [25]. In these cases, fluid resuscitation is a first line therapy to improve tissue hypoperfusion. Fluids are necessary to achieve and maintain goal central venous pressure, mean arterial pressure, urine output and central venous oxygen saturation [26].

Patients with SDSS (dysfunctional syndrome of stomatognathic system) in complementary pathology area but in a stabilized level, have been applied a mobile typology of prosthetic treatments, as well as relaxation mouth guards, an improvement of the quality of life of these patients being registered, as it follows: in 3 patients were applied acrylic prostheses, only in 2 cases being used the method of relaxation mouth guards ,in association with oral medication in the clinical base of maxillo-facial surgery IASI [27-31].

Conclusions
In dental medicine, oral-maxillofacial and dental sepsis is an important public health issue and clinical challenge with a major impact on healthcare expenditure and resources.

Oral-maxillo-facial and dental sepsis represents a current and a much debated public health problem for Romania too, with large perspectives in the research regarding morbidity, etiologic factors, pathophysiology, risk factors and, not in the least important, the treatment.

Our study revealed a high prevalence of sepsis with dental and oral-maxillofacial point of entry and the most affected persons were males from rural area.

The physician should pay attention to the electrolyte abnormalities and acid-base status disturbances in patients with oral-maxillofacial and dental sepsis because these can lead to fatal consequences. Early recognition of acid-base status and main serum electrolyte disturbances has high importance for clinical management since it signals the gravity of the disease and the increase of death risk. Also, the physician should pay attention to the administered fluid and medications potentially associated with electrolyte abnormalities and acid-base status disturbances in patients with oral-maxillofacial and dental sepsis.

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