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# Sepsis Syndrome in Croatian Intensive Care Units: Piloting a National Comparative Clinical Database

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**Aim** To assess the incidence of sepsis in selected intensive care units (ICUs) in Croatia, isolates from blood cultures, and sepsis outcomes, and to compare the results with those from other European countries.

**Methods** In the pilot phase of the national comparative clinical database project, we included 24 ICUs – general, specialized, neonatal, pediatric, and adult – 18 from university hospitals, 3 from county hospitals, and 4 from city hospitals. By retrospective chart review, trained data collectors abstracted the data on the case mix, management strategies, and outcomes in patients consecutively admitted to ICUs. Central validation for incomplete, illogical, or inconsistent values is regularly performed to improve accurateness.

**Results** Of 5293 patients treated in 24 ICUs from November 1, 2004, to October 31, 2005, 456 (8.6%) were treated for sepsis syndrome or severe sepsis. The most common isolates from positive blood cultures were *Escherichia coli* (11.6%), *Pseudomonas* species (9.9%), and methicillin-resistant *Staphylococcus aureus* (9.3%). With the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of 10.0 and Sequential Organ Failure Assessment (SOFA) score of 2.4, the overall mortality for sepsis syndrome, severe sepsis, and septic shock was 29%, 35%, and 34%, respectively. When compared to university hospitals and county hospitals, city hospitals with the smallest gravitating population had significantly lower APACHE II and SOFA scores, but significantly higher mortality.

**Conclusions** Overall mortality of patients with sepsis syndrome in Croatian ICUs was high, but outcomes of their treatment were comparable with those in other European countries. Better education in triage and treatment strategies is needed, including better implementation of Surviving Sepsis Campaign guidelines.

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> **Received:** March 7, 2006
> **Accepted:** May 22, 2006

> **Croat Med J. 2006;47:404-9**

The sepsis syndrome, severe sepsis, and septic shock represent a major therapeutic and economic problem. In the intensive care units (ICUs) in the European Union (EU) member states, severe sepsis and septic shock result in 135 000 deaths per year with associated costs of €7.6 billion (1). The meeting of the European Society on Intensive Care Medicine in Barcelona in 1992 resulted in the Declaration on the need for standardization of diagnostics, treatment strategy, and outcome analysis in these patients (2). A large Sepsis Occurrence in Acutely ill Patients (SOAP) study provided data on the incidence of sepsis in the ICUs in EU member states, patients' characteristics, management, and outcomes (3). Data on the incidence of sepsis in central European countries are less available. The Croatian National Institute of Public Health collects the national data on the incidence of sepsis, but does not collect any additional data, such as those on treatment or outcomes. Also, the incidence data are considered to be incomplete (4).

The *croicu.net* project was started in November 2004 to fill the gap in documenting the case mix, treatments, and outcomes in Croatian ICUs (5). The still ongoing pilot phase rests on voluntary participation of 24 ICUs. The final aim is to establish a national clinical database that would inform policy and foster professional development through enabling comparative audits of ICUs nationwide. We analyzed the data collected through *croicu.net* from November 1, 2004, to October 31, 2005, to assess the incidence of sepsis in the Croatian ICUs participating in the project, isolates from blood cultures, and outcomes, and to compare Croatian data with those from other European countries.

## Methods

In the fall of 2004, 24 of a total of 120 ICUs in Croatia joined the pilot phase of the study within the *croicu.net* project. The ICUs are of different profiles, from neonatal and pediatric to adult, and from general to specialized. Eighteen ICUs are located in university hospitals, 3 in large or county general hospitals (50 000-100 000 gravitating population), and 4 in city general hospitals (5000-10 000 gravitating population). The participating ICUs roughly cover almost 1.2 million people, or a quarter of the total population of Croatia.

One representative from each ICU attended the initial meeting in the fall of 2004 where the project was explained in detail and representatives trained for data collection according to precise rules and definitions. All data collectors were resident or consultant physicians.

From November 1, 2004, all participating ICUs started to collect a set of data for each patient leaving the ICU. Abstraction is performed by filling out a form based on a retrospective chart review. The form contains each patient's identifier, type of admission, demographic data, and data on the case mix, management, outcome, and length of hospital stay. Each participating ICU received a software for automatic score calculation, along with the Surviving Sepsis Campaign guidelines. The software for calculation of Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores for adults, and Pediatric Index of Mortality (PIM) 2 and Neonatal Therapeutic Intervention Scoring System (NTISS) scores for children and neonates, allows for data entry directly into the form (6-8). It has been estimated to take 8-20 minutes to abstract the data for one patient, depending on the abstractor's experience and the amount of interventions that the patient received.

Data are collected on consecutive admissions and uploaded on *croicu.net* by each participating ICU. Every three months, data are checked centrally for completeness, illogicality, and inconsistencies. Cumulative reports, also available online, are sent to each participating ICU. In the pilot phase of the project, all participating ICUs have access only to their own data and report analyses.

We report on the sepsis syndrome data collected during the first year of the ongoing project, from November 1, 2004, to October 31, 2005.

### Definitions

Sepsis syndrome was defined as a confirmed or presumed (all blood cultures negative) infection with fever of 38°C or hypothermia of 35.5°C, tachypnea of 20 or more inspirations/min, tachycardia of 90 beats/min or more, leukocytosis >10 000 white blood cells or bands over 10, and positive blood culture finding. Sepsis was diagnosed when at least two of these parameters were found in a patient. Severe sepsis was defined as sepsis syndrome with failure of two organs. Septic shock was defined as circulatory instability in sepsis, ie, hypotension of <100 mm Hg despite volume replacement (9).

### Statistical analysis

For statistical analyses, we used $\chi^2$ test for discrete variables and Kruskal-Wallis test for continuous variables. $P<0.05$ was considered to be statistically significant. We used MedCalc (MedCalc Software, Mariakerke, Belgium) software for all analyses.

## Results

Over the one-year period, a total of 5293 patients were hospitalized in the 24 ICUs. With 8.6% of all admissions (456 patients), sepsis and severe sepsis were the third most common reason, closely following myocardial infarction and pulmonary edema, for admission in the included ICUs (Table 1). With respect to the case mix, there was a significant difference in APACHE II score and SOFA score between the university, county, and city hospital-based ICUs. APACHE II score and SOFA score were significantly higher in university and county hospital ICUs than in city hospital ICUs ($P<0.001$) (Table 2). These differences were even more pronounced after coronary care units were excluded from the analyses. Overall mortality and mortality in patients with sepsis was significantly higher in the city hospital ICUs than university and county hospital ICUs (Table 3). These differences were even more pronounced after coronary care units were excluded from the analyses. The most common isolates from positive blood cultures in patients with sepsis syndrome were *Escherichia coli* (11.6%) and Pseudomonas species (9.9%) (Table 4). In all three groups of ICUs, >70% of patients with sepsis syndrome had sepsis at admission, whereas the rest of the patients developed sepsis during hospital stay (Table 5). The three groups of ICUs did not significantly differ according to the percentages of patients who were admitted with sepsis or developed sepsis during hospital stay.

**Table 1.** The most common 10 diagnoses of patients admitted to the 24 intensive care units (ICUs) in Croatia from November 1, 2004, to October 31, 2005

| Diagnosis | No. (%) of patients |
|---|---|
| Myocardial infarction | 592 (11.2) |
| Pulmonary edema | 542 (10.2) |
| Sepsis and severe sepsis | 456 (8.6) |
| Coronary artery bypass graft | 396 (7.5) |
| Renal failure | 373 (7.0) |
| Abdominal neoplasm surgery | 357 (6.7) |
| Other abdominal surgery | 344 (6.5) |
| Shock | 305 (5.8) |
| Tachyarrhythmia | 276 (5.2) |
| Respiratory insufficiency | 256 (4.8) |
| Total | 3897 (73.5) |

**Table 2.** Characteristics, mortality, and length of stay of patients admitted to university, county, and city hospital-based intensive care units in Croatia from November 1, 2004, to October 31, 2005*

| | Mean±SD for type of hospital† | | | |
|---|---|---|---|---|
| Parameter | university | county | city | Total |
| No. of patients | 3794 | 602 | 897 | 5293 |
| No. (%) of men‡ | 2314 (60.1) | 365 (60.6) | 457 (50.9) | 2509 (59.4) |
| Age (y)† | 60 ± 18 | 64 ± 16 | 63 ± 17 | 60 ± 17 |
| APACHE II score† | 11.1 ± 6.4 | 11.1 ± 6.6 | 5.6 ± 6.5 | 10.0 ± 7.6 |
| SOFA score† | 3.1 ± 3.0 | 1.3 ± 1.9 | 0.5 ± 1.5 | 2.4 ± 2.9 |
| Length of stay (days) † | 4.9 ± 5.4 | 4.1 ± 5.5 | 4.1 ± 6.0 | 4.8 ± 6.4 |
| No. (%) of deaths‡ | 448 (11.8) | 69 (11.5) | 110 (12.3) | 627 (11.9) |

*Abbreviations: SD – standard deviation; APACHE – Acute Physiology and Chronic Health Evaluation score; SOFA – sequential organ failure assessment score; ICU – intensive care unit.
†Kruskal-Wallis test, $P<0.001$ for all in adult ICUs.
‡$\chi^2$ test, $P<0.001$ for proportion of men and $P=0.451$ for proportion of deaths in adult ICUs.

## Discussion

A large European SOAP study provided extensive comparative data on sepsis syndrome in Eu-

**Table 3.** Patients with sepsis, severe sepsis, and septic shock and mortality rates in 24 intensive care units according to the type of hospital*

| Diagnosis | Mean±SD for type of hospital | | | Total | *P* |
|---|---|---|---|---|---|
| | university | county | city | | |
| No. of patients | 3794 | 602 | 897 | 5293 | |
| No. (%) of deaths | 448 (11.8) | 69 (11.5) | 110 (12.3) | 627 (11.9) | <0.001‡ |
| Sepsis: | | | | | |
| No. (%) of patients | 247 (6.5) | 22 (3.6) | 9 (1.1) | 278 (5.2) | <0.001‡ |
| APACHE II score | 18.2±5.2 | 16.3±7.3 | 16.1±5.4 | 17.9±6.2 | <0.001† |
| SOFA score | 6.3±1.5 | 5.2±2.0 | 5.3±2.2 | 6.0±1.9 | <0.001† |
| No. (%) of deaths | 71 (28.7) | 7 (31.8) | 5 (55.5) | 83 (29.1) | 0.001‡ |
| Severe sepsis: | | | | | |
| No. (%) of patients | 157 (4.1) | 15 (2.5) | 8 (0.8) | 180 (3.4) | <0.001‡ |
| APACHE II score | 20.1±4.9 | 18.8±6.1 | 18.9±7.4 | 19.5±6.2 | <0.001† |
| SOFA score | 6.9±3.4 | 6.1±2.5 | 6.1±3.0 | 6.8±3.4 | 0.002† |
| No. (%) of deaths | 52 (33.3) | 6 (40.0) | 5 (62.5) | 63 (35.0) | <0.001‡ |
| Septic shock: | | | | | |
| No. (%) of patients | 111 (2.9) | 14 (2.3) | 4 (0.5) | 129 (2.4) | <0.001‡ |
| APACHE II score | 21.3±4.9 | 19.9±5.4 | 19.7±5.0 | 21.0±6.1 | 0.008† |
| SOFA score | 7.2±3.1 | 7.1±2.8 | 8.0±4.8 | 7.3±3.2 | 0.127† |
| No. (%) of deaths | 36 (32.4) | 5 (35.7) | 3 (75.0) | 44 (34.1) | 0.045‡ |

*Abbreviations: ICU – intensive care unit; APACHE – Acute Physiology and Chronic Health Evaluation score; SOFA – sequential organ failure assessment score.
†Kruskal-Wallis test, adult ICUs only.
‡$\chi^2$ test, adult ICUs only.

**Table 4.** Isolates from blood cultures in patients with sepsis syndrome

| Infective agent | No. (%) of patients |
|---|---|
| *Escherichia coli* | 41 (11.6) |
| *Pseudomonas* spp. | 35 (9.9) |
| *Methicillin-resistant Staphylococcus aureus* | 33 (9.3) |
| *Klebsiella pneumoniae* | 16 (4.5) |
| Staphylococcus aureus | 16 (4.5) |
| *Proteus* spp. | 15 (4.2) |
| *Candida albicans* | 11 (3.1) |
| *Staphylococcus epidermidis* | 11 (3.1) |
| *Streptococcus pneumoniae* | 11 (3.1) |
| *Enterococcus* | 10 (2.8) |
| *Streptococcus* B-H | 9 (2.5) |
| Gram negative bacteria | 9 (2.5) |
| Methicillin-resistant *Staphylococcus epidermidis* | 8 (2.3) |
| *Enterobacter* spp. | 8 (2.3) |
| *Acinetobacter* | 7 (2.0) |
| *Hemofillus influenzae* | 4 (1.1) |
| All other | 25 (7.1) |
| Negative blood cultures | 84 (23.8) |
| Total | 328 (100.0) |

**Table 5.** Incidence of sepsis, severe sepsis, and septic shock on intensive care unit (ICU) admission and sepsis developed in the ICU according to the type of hospital

| Type of hospital | No. (%) of patients with* | |
|---|---|---|
| | sepsis on admission | sepsis developed in ICU |
| University | 382 (74.3) | 132 (25.7) |
| County | 37 (72.6) | 14 (27.3) |
| City | 15 (71.4) | 6 (28.6) |

*$\chi^2$ test, $P=0.926$.

ropean ICUs (3) and showed that sepsis was the reason for ICU admission in 37.4% of patients. The most common infection sites were the lungs and the abdomen, and the most common causative agents were *Staphylococcus aureus,* including methicillin-resistant form, *Pseudomonas*, and *Escherichia coli*. The overall mortality ranged between 18.5% and 24.1% and it depended on age, circulatory insufficiency, malignant disease, and positive fluid balance.

The *croicu.net* project provided for the first time data from Croatian ICUs that are suitable for national and international comparisons and should stimulate improvements in the management and outcomes of sepsis syndrome and policy making. Our data showed the overall incidence of sepsis syndrome in the included ICUs of 8.6% and overall mortality of 29.1%, similar to those recently published for the ICUs in the Republic of Slovakia (10). Total mortality rate in our patients with severe sepsis was lower than that reported in the literature, which can be explained by lower APACHE II and SOFA score in our patients. Similarly, the Episepsis Study found the incidence of severe sepsis in French ICUs of 8.4% and mortality of 56% (11). In Poland, a project similar to croicu.net that stemmed from the same project from the UK (12), start-

ed in 2003 and provided the first internationally comparable data for that country. Moreover, the project provided the first data ever on the incidence of severe sepsis in Poland. The study reported overall mortality of 55% (13). The mortality rate of the patients with septic shock and severe sepsis in our pilot study was the same, but the groups were too small to allow for any conclusion.

It seems that the incidence of severe sepsis and septic shock in ICUs in developed countries has increased in the previous years. In France, a prospective 3-year study found the incidence of severe sepsis of 42% (14). The same study showed that many patients developed sepsis during ICU stay rather than having it at admission and that mortality rates increased. In our pilot study, sepsis syndrome during ICU stay developed in 27% of all patients with confirmed sepsis.

Recording causative agents and their resistance to antibiotics is immensely important for future management and outcomes of sepsis syndrome, especially the continuous antibiogram monitoring (15). A Polish study recently found that the incidence of gram negative and gram positive causative agents in their ICUs was almost identical (13). The incidence of mycotic infections varies from about 20% in Polish ICUs (13) to about 4% in Croatia (this study). European epidemiological data showed that *Candida albicans* was the most common causative agent, most often in hematological patients, with a high mortality rate of 37.9% (16).

The most common isolates from positive blood cultures in the Croatian ICUs were *Escherichia coli*, *Pseudomonas* species, and methicillin-resistant *Staphylococcus aureus.* These findings are similar to those of the SOAP study. Other studies also observed a high incidence of gram negative causative agents, for example *Acinetobacter Baumanii* in patients with ventilator-associated bacterial pneumonia associated with previous antibiotic treatment, use of corticosteroids, and the need for renal replacement therapy (17).

Croatian ICUs systematically differed in the case mix and mortality rates. While patients treated in city hospital ICUs had significantly lower APACHE II and SOFA scores than patients treated in university and county hospitals, city hospital ICUs also had significantly higher mortality rates. Such findings point to the need for better triage of patients hospitalized in ICUs of smaller cities, which would also reduce cost, and for better education on treatment strategy, including the implementation of the Surviving Sepsis Campaign guidelines. However, our pilot analysis did not adequately adjust for the case mix in spite of APACHE II and SOFA scoring and thus does not permit for drawing firm conclusions.

The most common management of patients with severe sepsis in the Croatian ICUs was replacement of respiratory function (data not shown). Thus far, it seems that different forms of non-invasive mechanical ventilation, now available and recommended over invasive forms of mechanical ventilation (18), are used only sporadically in Croatia. On the contrary, it seems that continuous veno-venous hemofiltration was more common than intermittent hemodyalisis (19), although the most common form of extracorporeal circulation used for renal function replacement seems to differ between the ICUs (data not shown).

Our analysis suggests that the epidemiological data on the incidence of sepsis, length of hospital stay, and mortality should be considered at the individual hospital level rather than national level. The ongoing construction of clinical database should include all ICUs in Croatia and thus provide the platform for national comparative audits in the future. However, at this pilot stage, the variability of included ICUs does not permit robust comparisons and conclusions. Other limitations of our project currently include the lack of local control of data collection and data validation. Also, since the coverage of the Croatian population by the included ICUs is still uneven,

we are not yet able to calculate population-based parameters.

The Surviving Sepsis Campaign aims to reduce the severe sepsis mortality by 25% in 5 years, by disseminating and implementing generally accepted treatment guidelines (20,21). Croatia's participation in the campaign has the potential to improve the management and outcomes of sepsis syndrome, severe sepsis, and septic shock in Croatian ICUs. The provision of adequate comparative data has been a great challenge for us (22). We believe that *croicu.net* will, in the absence of a sepsis register, provide a robust basis for the national and international comparison of parameters and improve the management and outcomes of patients with sepsis syndrome in the Croatian ICUs.

**Acknowledgment**

This study was supported by the grant No. 57-400-000/05 from the Croatian Ministry of Science, Education and Sport (*croicu.net* project).

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