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THE RISK OF THE INFECTION AND THE SEPTIC COMPLICATIONS IN THE SURGICAL PATHOLOGY

-Thesis summary-

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Infection has always been part of the human life and in the modern surgery the sepsis continues to be a challenge for the physicians from the entire world. The study of the infectious risk and the postoperative infectious complications is absolutely normal in an age dominated, on one hand by the control of the financial resources for the health services and, on the other hand, by the bigger attention paid to the increase of the quality of these services; namely, the introduction of the rates of the hospital-acquired infections as an indicator of the quality care in a hospital.

Over the years, the population in question was considered especially the hospitalized patients, and the terms used were those of the hospital infection and the nosocomial infection. Today it is the preferred the term *healthcare associated infection* - HAI, as these infections can be gotten or can be associated with any unit in the system for providing health services, including the areas with the ambulatory patients or the centers of chronically care. On the other hand, the development of the acquired infections in the hospital may also occur at home, so after the discharge, such as the surgical wound infection, which can occur in four weeks from the surgery.

The hospitals in Romania, almost always underfunded and inadequately managed, the surgeon faced with complex problems of diagnosis and surgical treatment of a population of patients increasingly larger and with more serious pathology, is placed recently in the position to respond publically to the concerns about security and safety of the operated patient, beyond the familiar territory of the surgery room or the hospital.

This paper comprises two separate studies, which have different objectives. The first study sought to evaluate the postoperative infectious risk in three different surgeons: orthopedic, ENT and general surgery, to differentiate the patients using infectious NNIS risk index, calculated by summing the risk factors related to the patient (anesthetic risk score, given by the patient comorbidities) with others related to the surgery (the contamination class of the surgery and the duration of the surgery); these data are at hand in any surgical service, being usually recorded on sheets of anesthesia and observation . The second study aimed to evaluate the risk factors for the nosocomial sepsis in operated patients (without taking into account the kind of surgery), later hospitalized at the intensive care service. We considered that the special pathology and the exposure to different risk factors justify a different approach of the study of a feared complication, where the indices of mortality are increasd and hospital costs are much higher.

The thesis contains a total of 304 pages and is divided into 15 chapters. In the first 6 chapters, which belonged to the general part, I tried to synthesize the most relevant aspects of the complex issue of the infections associated to the health cares and antibiotic resistance of germs that are their etiologic agents. The following 8 chapters belonged to the part of the personal research, the study on postoperative infections in the surgical wards and the nosocomial sepsis study in patients at intensive care. The last chapter includes a program with prophylactic measures of the postoperative infectious complications, whose recommendations were based both on recent data from the specialized literature and information from the two studies.

Chapter 1 contains generalities on the issue of healthcare associated infections (HAI) in the world and in Romania; the analysis is discussed in terms of morbidity, mortality and costs. If we consider only U.S. hospitals, HAI was estimated in a study in 2002 to approx. 1.7 million cases. Of these, over 410,000 cases were in the ICU unit for children and adults and more than

1,250,000 cases out of intensive care units. The estimated number of deaths associated with HAI was 98,987 cases **(1).** The annual growth of hospital costs because of them were estimated to a range between 2 (**2**) and $ 3.5 billion / year **(3).** A report in 2009 **(4)** indicates that from 1,939,111 patients hospitalized in Pennsylvania (U.S.) in that year, 23,287 - 1.2%, patients had infectious complications (HAI) during their hospitalization. Their mortality rate was 9.4%, while at the patients with no such complications; the mortality rate was 1.8%. The average length of hospitalization in patients with HAI was 21.6 days, while at those without complications were only 4.9 days. For our country, data published by the Ministry of Health for 2008, data resulting from the current system of surveillance of these infections in the hospitals, reveals a small number of reported infections, respectively 9,677 cases **(5).**

In **Chapter 2,** we synthesized the data on the epidemiological features of HAI, showing that, as in all infectious processes, the imbalance of the ecological model, where either ***the pathogen or the characteristics of the host influence the normal ecological balance***, is the condition which leads at the validation of the infection at the level of the susceptible host; the medical care itself increases the risk of acquiring an infection in different ways: the direct contact with the specific pathogens in the hospital, an opening a breach in the skin (intravenous devices or surgical wound) or on the mucous surfaces (endotracheal intubation, urinary catheterization), the introduction of foreign bodies, the altering of the natural flora with the antibiotics or the treatment with the immunosuppressive drugs.

The physiopathological peculiarities of the healthcare associated infections were discussed in **Chapter 3**. After reviewing the data of the general physiopathology of the infections in **section 3.1**, where it was stated that the pathogenetic process of developing an infection, in most of the cases, has several stages, being influenced by the involved infectious agent, by the way and the place of contamination, by the inoculum size, by its virulence and by the immune status of the host, we continued in **section 3.2** presenting the pathophysiology of the nosocomial infections, showing that the development of the nosocomial infection is linked to two key factors: the decreased efficiency of the host defense mechanisms and the colonization with the pathogenic or potentially pathogenic microorganisms. Even if these factors can exist independently, their simultaneous presence in certain proportions is *the necessary condition* for the development of the infection. The immunosuppression, a particularly characteristic of the patients hospitalized at intensive care services due to generally download interleukin 10 and other anti-inflammatory mediators (such as interleukin-1 receptor antagonist and tumor necrosis factor TNF), creates a state of "immune paralysis" **(6),** which is associated with an increased risk of infection. The invasive maneuvers as endotracheal intubation also affect the local defense mechanisms: cough, sneezing, mucociliary clearance. The bacterial colonization, either exogenous (hospital flora) or endogenous (patient's own flora) is also closely related to hospitalization, being characteristic to the patients with serious diseases, whose defense mechanisms are down, the presence of the various forms of invasive devices forms places of bacteria, while the broad-spectrum antibiotics is frequently and for long periods done.

Chapter 4 approached the issue of the risk factors for the healthcare associated infections, systematized on three areas: the risk factors related to the health of the host, the risk factors

related to the severity of the underlying disease and the risk factors related to the complexity of the therapeutic actions during the hospitalization.

In **Chapter 5** we present the main clinical syndromes in the healthcare associated infections, pointing out the sepsis **(section 5.1.2)** and the postoperative wound infections **(section 5.1.3)** and pneumonia **(section 5.1.1)** and the urinary tract infections **(section 5.1.4.),** pointing out the definition, pathogenesis, etiology and positive diagnosis for each of these entities.

In the case of *the sepsis* (BSN), it was stated that it is the inflammatory systemic response which results from the inability of the immune system to limit the bacterial invasion after the onset of the infection and carries a risk of poor outcome; the majority of the nosocomial bacteremia results in sepsis, the percentage could rise in some studies up to about 80% **(7).** The question in such studies is whether the nosocomial sepsis is a primary bacteremia or a systemic reaction that accompanies other unrecognized infection or a noninfectious inflammatory response **(8, 9).** The significance of the bacteremia results only if there are differentiated the true pathogens from the bacterial flora (skin) of contamination. The most common place for the infection to get inside is the vascular catheters, namely the insertion place of the catheter, with the infection spread, initially, along its outer surface **(10, 11).**

The evaluation of the fever at an operated patient must include careful evaluation of the surgical wound. *The postoperative nosocomial infections* (PONI) can be localized at the level of he wound or may occur away from the operation place (urinary, catheter, respiratory, bacteremia). They can be installed within a variable up to 30 days before their surgery, or even 1 year (implants). The various clinical manifestations make it difficult to define PONI accurately. In the United States, to standardize the data resulted from the surveillance, in 1992 **(12)** CDC has classified PONI in **surgical incisional wound infections**, which can be surface- PONI S (skin and subcutaneous tissue limited by supra aponevrosis fascia) or deep-PONI P (the muscle or other tissues beneath this fascia) and **space / organ surgical infection – PONI SO**, affecting any part of the body which was handled during the surgery. This classification was also adopted by the surveillance system from our country **(13).** The type of surgical procedure itself involves several degrees of risk, that is why the surgical wounds that have been classified in clean, clean-contaminated, contaminated and dirty-infected **(14).** Combining the five classes of *risk ASA* (established preoperatively by the anesthesiologist) with *the class of the contamination of the wound* and with *the duration of the surgery* it is obtained **the risk score NNIS (14, 15, 16)** to estimate the individual postoperatory infectious risk (Table no.1). The NNIS risk score integrates practically the 3 main determinants of the infection: bacteria (the presence of the contamination), environment (the surgical wound) and the host defense. Other risk factors are not included in this score, even if they are relevant to the clinician in assessing the infection risk (smoking, blood sugar, obesity, shock, hypothermia, etc.).

Table no. 1

The necessary elements to calculate the risk score NNIS

The duration of the surgery over the time limit (in minutes) for the type of the intervention	**1 point**

Wound classification: class III or IV	**1 point**
Score ASA ≥ 3	**1 point**
Risk index NNIS	**0-3**

In **Chapter 6** we presented the problem of the antibio-resistance and of the resistance mechanisms to antibiotics, with emphasis on multidrug resistant organisms (MDRO), including methicilin-resistant Staphylococcus (MRSA), vancomicin-resistant enterococci (VRE) and some gram negative bacilii (BGN), which have very important implications in the hospital control of the infections. In **section 6.2** we centralized the general data about the importance of antibio-resistance problem worldwide and in Romania, based primarily on the data contained in the reports of the European Antimicrobial Resistance Surveillance System (EARSS) **(17).** These reports placed Romania (Table no.2) in 2009 to levels of methicilin-resistance staphylococci above 35%, multidrug-resistant strains of Klebsiella 11.1% and of the Pseudomonas bacillus 36%.

Table no. 2

The proportion of non-susceptible isolated to antibiotics (%) over the years 2002-2009 in România

Pathogen and antibiotic class	2002	2003	2004	2005	2006	2007	2008	2009
SAH MRSA								
Methicilin R	36	46	71	60	54	26	33	36
E. coli								
AminopenicillineR	50	70	79	78	85	76	55	83
Aminoglicosyde R	15	21	33	14	41	35	24	13
Fluoroquinolone R	20	14	21	9	41	27	27	23
Cephalosporine gen IIIR	18	19	23	17	41	27	24	17
Klebsiella pneumoniae								
Aminoglicosyde R	-	-	-	100	91	80	60	31
Fluoroquinolone R	-	-	-	33	34	23	20	11
Cephalosporine gen IIIR	-	-	-	100	94	80	50	56
Pseudomonas aeruginosa								
Piperacillin R	-	-	-	61	33	25	25	36
Ceftazidime R	-	-	-	52	-	-	13	38
Carbapeneme R	-	-	-	61	-	-	13	55
Aminoglicosyde R	-	-	-	64	33	25	38	45
FluoroquinoloneR	-	-		64	33	25	25	36

According to ***Antimicrobial resistance surveillance in Europe*** *Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), 2009* **(17)**

In **section 6.3** we presented the general mechanisms of bacterial resistance to antibiotics, pointing out the available data for all classes of antibiotics.

In **The Personal Research** we studied two types of infectious complications in operated patients: the infections of the postoperative wound and the nosocomial sepsis. The research was conducted separately for these clinical entities and was structured into two distinct parts. The first study is entitled "Research on the Risk Factors and the Etiology of the Operating Wound Infections in General Surgery, Orthopedic and ENT" and the second is entitled "Research on the Nosocomial Sepsis in Intensive Care Operated Patients". At the end of the two studies, the discussions and the final conclusions were approached together in one chapter.

Study I. Research on the Risk Factors and the Etiology of the Operating Wound Infections in General Surgery, Orthopedic and ENT

In **Chapter 7** we presented the working hypothesis, which assumes that at the level of a health unit, the knowledge of the incidence of the postoperative infections, of the associated risk factors and of the etiologic spectrum specific to each surgical service are the factors that can lead to the major desire to reduce the postoperative infectious complications and therefore of the hospitalization costs. The purpose of this study was to obtain the data necessary for the carrying of a control programme of the infectious complications after surgery, its application aiming to improve the quality of the medical care in the surgical wards by reducing the infectious risks.

The objectives of the study were: the assessment of the incidence of the postoperative infections in the departments of General Surgery, Orthopaedics and ENT from an emergency hospital; the identification of the main risk factors and the assessment of their magnitude in the postoperative infections; the identification of the etiologic agents of the postoperative infections and of their spectrum of the antibiotic resistance in the surgical wards.

The study material **(Chapter 8)** was represented by a particular study group of patients from County Emergency Hospital in Sibiu, hospitalized between January 1st 2008 - December 31st 2010 at General surgery wards, orthopedics and ENT and who were diagnosed with postoperatory infection. During this period, there have been hospitalized a total of 16,310 patients, of which a total of 13,080 were operated on, the rest being discharged without undergoing surgery. Of the 13,080 patients with surgery performed in the three sections, the study has only taken in consideration the following categories of interventions:

a. general surgery:

• Exploratory laparotomy.

• Abdominal surgery, surgical cure of hernia, eventrations and eviscerations

• Cholecystectomy

• Biliary, liver and pancreas surgery,

• Bowel, colon and rectum surgery: appendectomy, segment enterectomia, etc. hemicolectomia.

• Surgery esophagus, stomach, duodenum: resection anastomosis gastric ulcer or gastro-jejunal, etc. gastrectomy.

• Spleen surgery

• Thyroid surgery

• Peripheral vascular surgery

b. in orthopedic surgery:

• Primary hip arthroplasty, total or partial

• Primary knee arthroplasty

• Revision hip arthroplasty

• Revision knee arthroplasty

• Upper and lower limb fracture fixation

• Fixation with external fixators

c. ENT surgery:

• Interventions of laryngeal endoscopy, suspended laryngoscopy

• Tracheostomy

• ENT pathology in oncology (nose, mouth, larynx, ear tumor), laryngectomy (total, partial) removal of cervical lymph nodes.

Thus were selected a total of **318** patients with ENT interventions, **2624** with orthopedic surgery and **4656** patients with general surgery interventions, finally being **7598** operated patients.

Among the operated patients, a number of **187** were diagnosed with wound operatory infections, of which 8 had two surgical wound infections during hospitalization, with the change of the etiological agent, they are practically counted twice. We found that there were a number of **195 cases of PONI**, which constituted the **study group**.

The control group consisted of the remaining 7411 patients, who were hospitalized and operated in the same period at the sections of General Surgery, Orthopaedics and ENT of County Emergency Hospital from Sibiu and who, postoperatively, *did not have infectious complications* at the level of the surgical wounds. Of these, we selected a representative **subset of witnesses**, to study the risk factors associated with the postoperative infection, by their comparing them with the lot of the cases. The selection of the patients who were the **subset of witnesses** was randomized using a computer program (Random Number Generator) (**18**), which allowed us to randomly select a number of **251** patients from the 7411 ones.

The methodology, described in **section 8.2**., included the definition of a protocol regarding **the methodology of the gathering data (8.2.1.),** pointing out the main steps in Fig. 1.

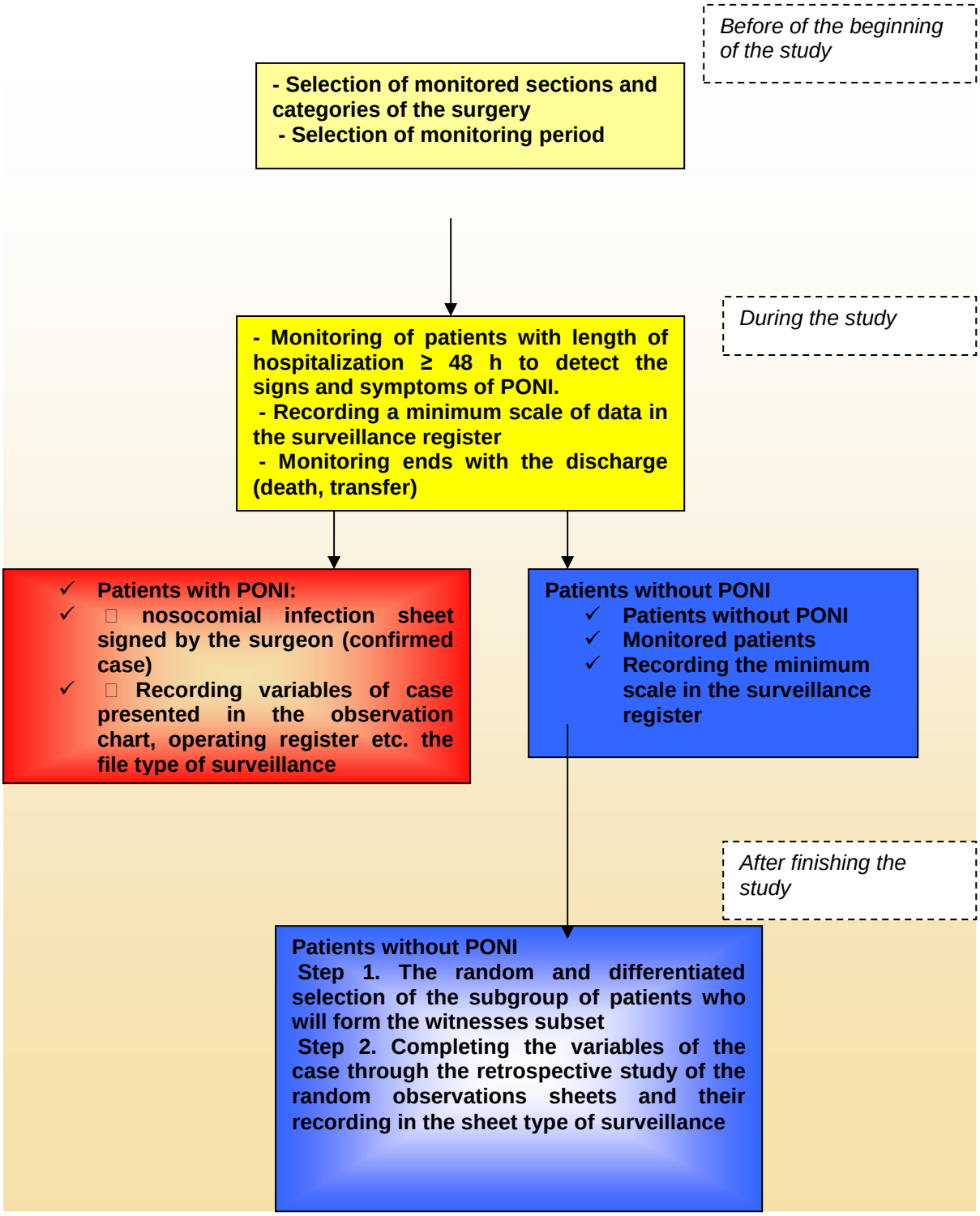


Fig. no. 1 Work methodology: the main steps in monitoring the sections and gathering the data of the patients

The definition of investigated variables was the objective of the subchapter 8.2.2., from 8.2.2.1 to 8.2.2.17, the following variables are defined: number of preoperative hospital days (as a measure of the preoperative colonization of the patients with hospital germs), the number of the days of the postoperative hospitalization in the ICU ward (as a measure of the additional risk of the bacterial colonization and of the exposure to invasive maneuvers specific to this duty), the presence of the preoperative anemia (the result of the decreasing of the amount of

oxygen in the blood and at the level of the tissues), ASA score (the quantification of the preoperative comorbidities present in patients), the presence of the diabetes, the presence of he perioperative hyperglycemia, the presence of the obesity, the presence of the diagnosis of neoplasia. The risk of surgery act was analyzed using variables: duration of surgery, type of surgery (conventional or laparoscopic), class of contamination of intervention, and the character of the emergency of the intervention, the prophylactic antibiotics preparation, the presence of the multiple procedures performed through the same surgical incision. To compare various risk factors, we grouped the patients from the two lots by calculating the risk index NNIS.

After gathering the data, the work methodology has consisted of the following main coordinates:

 in section 8.2.3.: **The methodology of the microbiological diagnosis of PONI**

For the microbiological diagnosis of PONI was developed in collaboration with a microbiologist, a specific protocol whose main steps were: 1. *Taking the samples of the pus* 2. *The transport of the samples* 3. *The laboratory examination*, 4. *The isolation and identification* 5. *Testing the sensitivity to antibiotics*.

 in section **8.2.4**. **The methodology of the analysis of the incidence PONI in the monitored wards** This analysis was made possible through a ***cross-sectional study***, which aimed to measure the incidence of PONI and the comparison of the results with the public data from Romania and from countries where good surveillance systems exist (countries in Europe and the United States of America).

The incidence was defined as the number of new cases of PONI appeared in the study period reported to the total number of operated patients, who had one of the monitoring interventions in the three sections.

 in section 8.2.5 The methodology of the analysis of the risk factors for PONI The analysis of the risk factors for the appearance of PONI was realized through a ***case-control type study***, prospectively, which allowed us to assess the of their impact in the appearance of PONI.

 in section 8.2.6 The methodology of the analysis of the etiology and of the antibiotic resistance problems of the isolated germs from the patients from the study group. The analysis of the bacterial and fungal etiologic spectrum of PONI and of antibio-susceptibility phenotypes of the etiologic agents was achieved through a descriptive study.

 in section 8.2.7 The methodology of the processing of the statistical data. The database has been developed in Excel. The data were exported in the Medcalc program, which was used for primary and advanced statistical analysis. The realization of the graphs was done by using both the mentioned programs. The statistical analysis protocol included as a first step the formation of the database by entering in two Excel files of the data regarding the study group and the control subgroup. The second step of the protocol was to export the two files (study group and subgroup control) in the Medcalc statistical and graphical processing program. In this program, we made the univariate primary statistical analysis and the multivariate statistical analysis. The statistical analysis of data followed the measurements of the central tendency and variability. The comparison of variables was done either by using parametric Student test for

those with normal distribution or nonparametric Mann Whitney test for those with nongaussian distribution. The qualitative variables were transformed into dichotomous variables and were compared using frequency tables and chi square test. The correlations between the presence of PONI and several variables were tested by calculating the rank correlation (Spearman rank correlation coefficient). To test the relationship between the presence of the disease and the values of some parameters, we made frequency tables and used chi square test. The multivariate statistical analysis was performed by logistic regression test to assess the relationship between the dichotomous dependent variable (presence or absence of infectious complications) and several independent variables that can influence these complications. Whatever the method of analysis, the differences or the results were tested and interpreted by the value of P ("P value"), considering the statistical significance level P less than 0.05.

In **Chapter 9** we presented the results of the investigations and the performed statistical analysis.

The results of the analysis of the incidence PONI in the monitored wards (section 9.1.) showed that the overall incidence of PONI during 2008-2010 was of **2.56%,** reporting the total number of PONI to the total patients operated in the general surgery wards, orthopedics and ENT. The most PONI appeared in 2008. To make comparisons with the data from other international surveillance systems (Table no. 3), we used he data published by the American surveillance system (NHSN) **(19),** data from European surveillance system HELICS IV **(20)** and data from the surveillance system from England **(21).**

The colonic surgery was the category of surgery that had the highest rate of incidence of PONI, with values of 10.91%; it is within the ranges of values published by other European countries (7.9 to 12.3%) or the U.S. (3.99 to 9.47%). The stomach surgery (9.52%) and the rectum surgery (8.77%) occupied the second and third places as incidence, being within the range of values published by other European countries or the U.S. (3.47 rectal surgeries - 26.67% in U.S., 9.9% for stomach surgery in England). PONI in the clean orthopedic surgery had incidence rates up to 3.15%: the incidence of the hip arthroplasty (1.81%) was comparable with other European countries values (1.5 to 3.4%) or U.S. (0.67 to 2.40%); the incidence of the hemiartroplasties was higher (3.15%), but comparable with values in England (4.9%). In ENT surgery, PONI incidence was 2.51%, a level which is within the range of values resulting from the U.S. surveillance system (1.64 -11.40%).

Table no. 3

Comparison among the PONI incidences, depending on the type of surgery

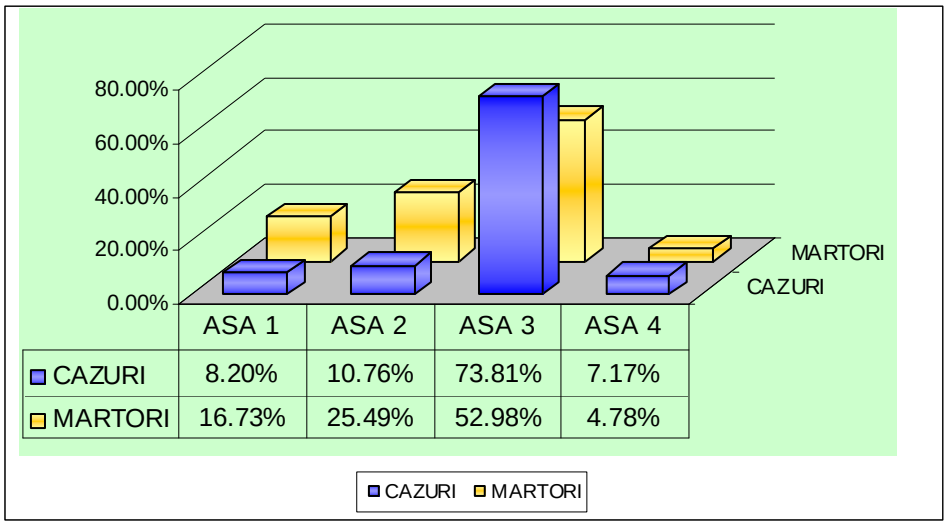
No.	Type of Surgery	Incidence NHSN	Incidence HELICS IV					Incidence Great Britain	Incidence SCJU Sibiu
			DE	FR	PL	NL	BE		
1.	Amputation of an arm	1,25-3,04						14,9	6,35
2.	Appendectomy	1,15-3,47							1,15
3.	Biliary, liver and pancreas surgery	8,07-13,65						11,3	5,12
4.	Cholecystectomy	0,23-1,72	1,5	1,0	1,4	2,0	5,3	4,1	1,14
5.	Peripheral vascular surgery	2,93-6,98						6,7	2,00
6.	Colon surgery	3,99-9,47	7,9	9,3	6,8	11,7	12,3	9,3	10,91
7.	Gastric surgery	1,72-4,23						9,9	9,52
8.	Surgical cure of hernia	0,46-5,25							2,02
9.	Abdominal hysterectomy	1,10-4,05						2,0	2,38
10.	Rectal surgery	3,47-26,67							8,77
11.	Bowel surgery	3,44-6,75						10,1	2,77
12.	Spleen surgery	2,33							6,25
13.	Thyroid surgery	0,26							1,66
14.	Abdominal exploratory laparotomy	1,67-2,82							6,52
15.	Open reduction of the fractures	1,11-3,36						3,8	1,27
16.	Total hip prosthesis	0,67-2,40	1,5	2,1	3,4	2,9		2,2	1,81
17.	Hip hemiartroplasty							4,9	3,15
18.	Prosthetic knee	0,58-1,60						1,4	2,38
19.	Neck surgery	1,64-11,40							2,51

DE=Germany, FR=France, PL=Poland, NL=Netherlands, Be=Belgium
*Data from the systemsof the surveillance NHSN (**19**), HELICS IV(**20**) and SSI Surveillance in England (**21**)*

In **section 9.2.** we presented **the results of the analysis of the risk factors for PONI** obtained by a case-control study. We attempted to quantify each risk category, both those related to the patient and to the operator act, to describe them in a first step, then, in a second step, to be measured by comparison with a control group of patients operated and uninfected, randomly chosen.

In *general surgery interventions*, the patients with PONI were **older** than those without infection **(P = 0.0215).** Across the whole cohort of operated patients (all types of surgeries), there was a **statistically significant positive correlation between the presence of PONI and the patients over 50 years old (P = 0.0178).**

There were significant differences in the distribution of **ASA scores** (fig.no.2) at the two groups **(P <0.0001).** This difference remained significantly in the analysis by types of surgery for the patients who had general surgery interventions. There were statistically significant **negative correlations between ASA score 1 and 2 and the presence of PONI (P = 0.0080, respectively P <0.0001) and a statistically significant positive correlation between ASA 3 and 4 and the presence of PONI (P <0.0001).**



	ASA 1	ASA 2	ASA 3	ASA 4
CAZURI	8.20%	10.76%	73.81%	7.17%
MARTORI	16.73%	25.49%	52.98%	4.78%

Fig no. 2 Percentage distribution of ASA scores in the group cases and witnesses group

The preoperative anemia was present in 43% of the patients with PONI and at only 25% of those without infectious complications, the difference being statistically significant (**P = 0.0001), there is a direct statistically significant correlation between the presence of the anemia and the PONIdiagnosis (P <0.0001)**. The values of **the haemoglobin** (fig.no.3) and of the **hematocrit determined preoperatively** at the group of the infectious complications were significantly lower than in those without such complications **(P = 0.0343 and p = 0.0028).** Both in cases and in witnesses, the patients with anemia had mostly mild disease. **We found that there is an inverse correlation, statistically significant between the values of the haemoglobin and of the hematocrit and the presence of PONI (P <0.0001). Also, there is a direct and significant correlation between haemoglobin values lower than 8.1 g / l and the frequency of PONI (P = 0.0012).**

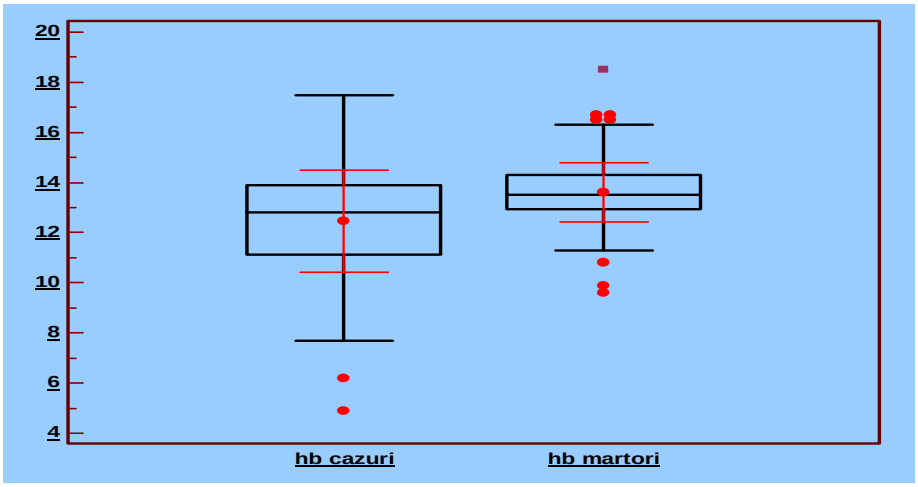


Fig no. 3 Haemoglobin levels at the study group and the witness subgroup (arithmetic mean ± 1Ds), P = 0.0343

There were significant differences regarding the presence of diabetes in patients who had PONI, than in those without infectious complications at the level of the operating wounds **(P = 0.0003)**, with **statistically significant positive correlation between the presence of PONI and the presence of diabetes at the operated patients (P = 0.0002). The perioperative blood glucose which exceed the normal values 112g/dl, 125g/dl and 155 g / dl correlated positively with the presence of PONI (P = 0.0396, P = 0.0019 and p = 0.0003).**

In patients who suffered *orthopedic surgery* was a **greater number of preoperative hospital days** in cases with infectious complications, the difference compared with the witnesses, with statistically significant tendency **(P = 0.0618). In the case of the orthopedic surgery, there was a positive correlation, which tends to have statistical significance (P = 0.0603) between the number of days of preoperative hospitalization and the appearance of PONI.**

The number of the days of postoperatory hospitalization in ICU was statistically significant **(P <0.0001)** higher in patients with PONI than in patients without postoperative infections. In the analysis by category of surgery, this significant difference is maintained for the general surgery interventions. **The correlation between the presence of PONI and the number of hospitalization days in the ICU is direct and statistically significant (P <0.0001).**

The difference between the average duration of the operations in the two groups was statistically significant (fig. no. 4) (**P = 0.0001**), in the case of the patients who developed PONI is higher; it was the same in the case of over time "T" - specific to each category of surgery was significantly higher in patients with PONI(P = 0.0063).

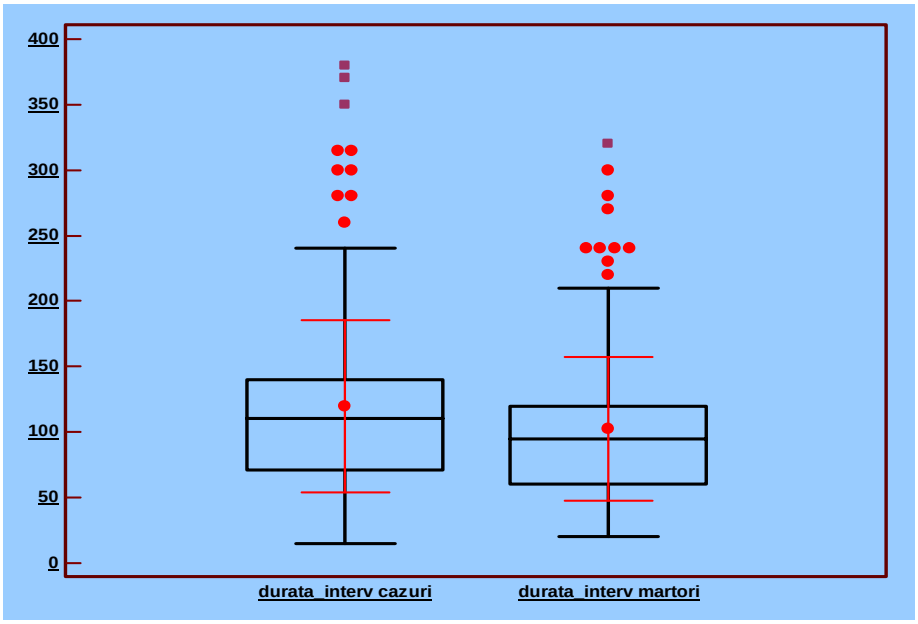


Fig no. 4 The duration of the surgery in the study group and in the witnesses group (arithmetic mean ± 1Ds), P = 0.0001

There were **significant positive correlations between PONI and the duration of operation (P <0.0001) and between PONI and over time "T" (P = 0.0043).**

In the group without postoperative infections, the number of the **interventions made with laparoscopy** was significantly higher compared to the group cases **(P = 0, 0347). The laparoscopic surgeries were inversely and significantly statistically correlated with postoperative infectious complications (P = 0.0203).**

The emergency surgeries were more common at patients with PONI, the difference at patients without PONI being statistically significant, **P = 0.0491**. This type be operated for the acquirement of the PONI: **OR = 1.6992, 95% CI = 1.0313 to 2.7996. The infectious complications are directly and significantly correlated with the performing of the emergency surgery on the operated patients (P = 0.0364).**

The most surgical procedures, both those with PONI and patients without PONI were from **the contamination classes 2 and 3. The wounds from the categories 3 and 4 as adegree of contamination were directly and significantly correlated (P <0.0001) with PONI at the operated patients.**

After the calculation of the NNIS score, we found that there is a significant statistical difference of infection risk between the two groups (Fig. No.5) **(P <0.0001)**, with a significantly higher risk of infection for the NNIS index 2 and 3 **(OR = 2.9520, respectively OR = 5.9048)**. **Between the NNIS risk small classes, 0 and 1, the correlations are inverse and statistically significant (P <0.0001, respectively P = 0.0429), and the larger classes, 2 and 3, correlate significantly positively with the presence of PONI (P <0.0001).**

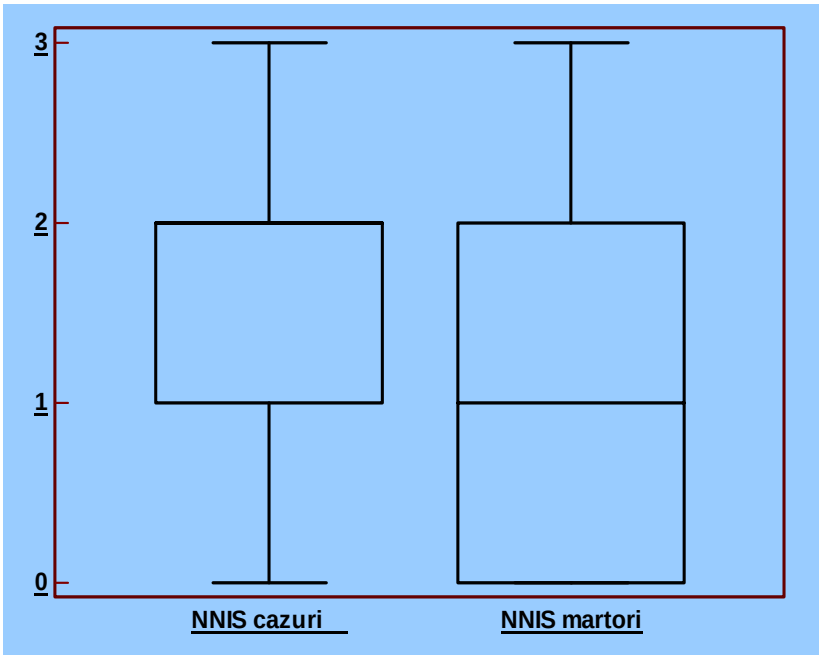


Fig no. 5 NNIS score in group cases compared to the subgroup (P <0.0001)

The risk of death was significantly higher among the patients with PONI than among those without PONI infection **(OR = 4.4107).**

The most surgical wound infections in group cases were **superficial and supra-aponevrotic infections (over 72%) (Fig no. 6)**

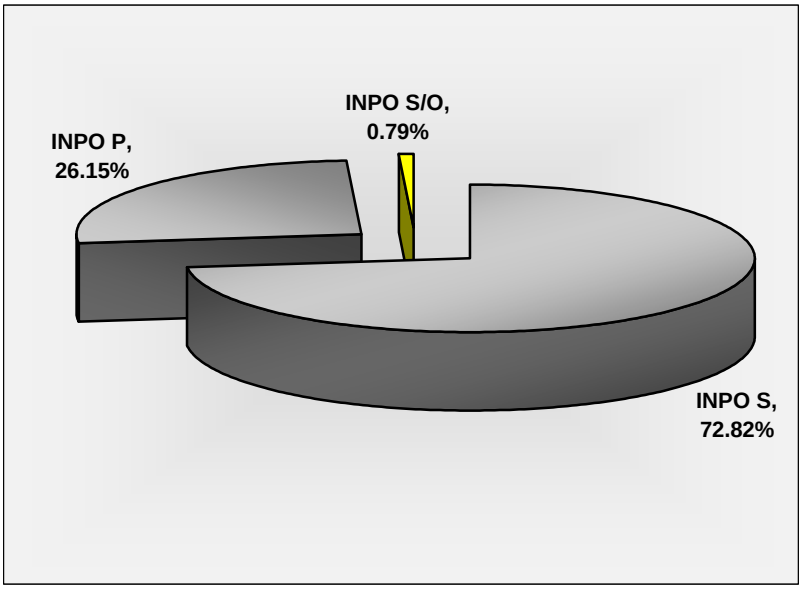


Fig. no. 6 The distribution of the types of PONI in the study group

The multivariate statistical analysis to identify the independent risk factors for the appearance of the postoperative infections of the surgical wound (section 9.2.3.)

The multivariate analysis was performed in two stages, first in the entire cohort of 446 operated patients, then separately in classes with NNIS infectious risk. As it has been shown a good correlation between the presence of the PONI and the four classes of risk of infection, they were used to separate the operated patients according to the categories of risk, and the separate performing of the multivariate analysis started from the premise that it is possible that the risk factors are not the same in patients of different risk categories. I tried, in other words, to create study models for the risk factors, taking into account the specific particularities of each individual patient and of the operator acts performed in the studied cohort.

If no adjustment is made for NNIS risk index, we found that the significant risk factors in the appearance of the postoperative infectious complications were the ***emergency surgeries*** **(P = 0.0125, OR = 2.3200)**, the presence of he ***diabetes diagnosis*** **(P = 0.0119, OR = 2.1129)**, ***wound contamination class*** **(P = 0.0001, OR = 1.8132),** ***the patient's comorbidities*** **(P = 0.0168, OR = 1.6371),** ***the prolonged postoperative hospitalization in the ICU*** **(P = 0.0022, OR = 1.2233)** and ***the surgery duration*** **(P = 0.0174, OR = 1.0050).** The postoperative hospital stay was a risk factor that tends to be significantly **(P = 0.0514, OR = 1.0520).**

When analyzing by groups of age, we found that at the patients younger than 50 years, the most important risk factors for acquisition of PONI were ***the prolonged hospitalization, over 48 hours in ICU*** **(P = 0.0001, OR = 3.0587)**, ***the perioperative blood sugar over 155mg/dl*** **(P = 0.0079, OR = 2.7449)**, ***the emergency operations*** **(P = 0.0070, OR = 2.6904),** ***the over time operator "T"*** **(P = 0, 0062, OR = 2.3092),** ***the wound contamination class*** **(P = 0.0000, OR = 1.9032),** ***the exceeding of 48 hours of preoperative hospitalization*** **(P = 0.0453, OR = 1.7598)** and ***the ASA score of the patient*** **(P = 0.0087, OR = 1.6543).** At the patients aged between 51 and 70 years the risk was significant for**:** ***age*** **(P = 0.0201, OR = 1.7018),** ***the prolonged hospitalization in the ICU over 48 hours*** **(P = 0.0000, OR = 3.2486),** ***the emergency of the surgery*** **(P = 0.0029, OR = 3.0453),** ***the hyperglycemia over 155mg/dl*** **(P = 0.0163, OR = 2.5089),** ***over time operator "T"*** **(P = 0.0072, OR = 2.2738),** ***the wound***

***contamination class* (P = 0.0000, OR = 1.9224*), the preoperative hospitalization over 48 hours* (P = 0.0276, OR = 1.8819)** and ***the association of the comorbidities*, ASA score (P = 0.0065, OR = 1.5756).**

In the subsections 9.2.3.2, 9.2.3.3 and 9.2.3.4, we performed he multivariate statistical analysis to identify the independent risk factors in the cohort of the patients with infectious risk NNIS 0 and NNIS 1, respectively, NNIS 2 and 3.

In patients with NNIS score 0, **the male sex and the multiple procedures performed during the surgery** were the significant risk factors for the acquisition of PONI (**P = 0.0221, OR = 8.8996,** respectively **(P = 0.0156, OR = 7.2617)** .

At the patient with NNIS risk, the significant risk factors for the acquisition of PONI were the emergency surgeries **(P = 0.0027, OR = 5.0745)**, the longer duration of the postoperative hospitalization in ICU **(P = 0.0248, OR = 1 , 3167)** and the prolonged preoperative hospitalization **(P = 0.0361, OR = 1.1137)**; the patients with an NNIS 1 risk index, from the age group between 31-50 years, are at the risk of acquiring PONI, this risk having a tendency of the statistical significance **(P = 0.09, OR = 2.2758).**

The significant risk factors for the acquisition of PONI in patients with NNIS risk score of 2 and 3 were: **the presence of the preoperative anemia (P = 0.0132, OR = 2.5492), the patient's diagnosis of diabetes (P = 0.0188, OR = 2.9518), the emergency surgeries (P = 0.0098, OR = 6.2937)** and **the prolonged hospitalization in the ICU (P = 0.0364, OR = 1.2117).** Also**, the hyperglycemia with values above 155mg/dl (P = 0.0116, OR = 15.0773), emergency surgeries (P = 0.0052, OR = 7.8800)** and **the patients aged between 51 and 70 years (P = 0.0146, OR = 2.4161)** are significant risk factors for the developing of PONI at the patients with NNIS risk 2 and 3; in the case of the patients with NNIS risk 2 and 3 who had elective surgeries, the significant risk factors for the infectious complications were; **the perioperative hyperglycemia over 155mg/dl (P = 0.0143, OR = 13.4282, aged between 51 and 70 years (P = 0.0394, OR = 2.0255) and the hospitalization in the ICU more than 3 days (P = 0.0256, OR = 2.5369).**

In **section 9.2.4**, we performed a detailed analysis of **the etiologic spectrum of the postoperative infectious complications.**

The etiological diagnosis was established in 193 of the 195 cases with PONI (98.97% of cases). These infections have started at various intervals of the time, within the range from 2 to 120 days postoperatively. There were isolated a total number of 260 microbial strains, of which only two (0.77%) were fungi, the rest of them were 258 bacteria, of which 182 (70%) strains were bacilli and 76 (29.23%) were cocci (Fig. no. 7).

Most of the isolated strains from the wounds were E. coli, the incidence PONI produced by this microbe being of 24.64%; the most infections of E. coli belonged to colon surgery. Over one third of the strains (35.41%) were in the secretory phenotype of β lactamases with extended spectrum (BLSE) and 50% from the strains had multidrug-resistance; the resistance was to three classes of antibiotics, aminopenicilline with IBL + cephalosporins 3$^{rd.}$ gen. + fluoroquinolones. 12.5% of strains were resistant to one class of the antibiotics (to aminopenicilline) and as many were resistant to four classes (IBL + aminopeniciline with cephalosporins 3rdgen.+

fluoroquinolones + aminoglycosides). The PONI rate produced by the strains of E. coli BLSE + decreased continuously from 41.17% in 2008 to 35.29% in 2009 to 23.53% in 2010, however, the decrease from 2010 compared to 2008 was not significant.

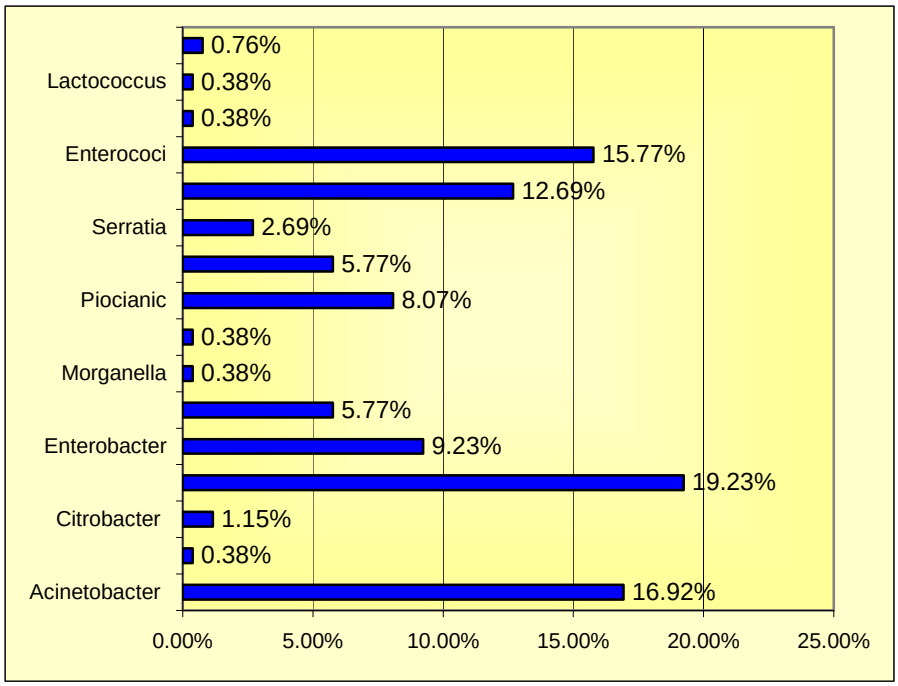


Fig. no. 7 The distribution of the microbial strains isolated from the surgical wound secretion

Acinetobacter baumannii ranked 2 as frequency between bacteria; most of the septic complications with Acinetobacter occured after the open reduction of the fractures; the incidence PONI produced by this microbe was 22.56. Over **88%** of the strains were multidrug-resistant, the dominant phenotype being the one of resistance to 3 classes of antibiotics, namely the cephalosporins 3rd gen.+ fluoroquinolones + aminoglycosides. **20%** of the isolated strains were carbapenem resistant; they were in 100% from the cases resistant to the 3rd gen. cephalosporins and 75% of the cases resistant to the aminoglycosides. The tendency of the annual incidence of the carbapenem-resistant strains was of **growing continuously**, the differences between the incidence data between 2008 and 2010 being statistically significant **(P = 0.04),** which is a real concern.

Other Enterobacteriaceae that produced PONI were Enterobacter (incidence 12.30%), Klebsiella (7.70%), Serratia (3.59%). A high percentage of the strains which contains β lactamases with a large spectrum were also present in the isolated Enterobacteriaceae from the surgical wounds: 54.16% for Enterobacter, 86.66% in Klebsiella, 57.16% from Serratia. In evolution, the incidence of the strains BLSE + remained constantly in 2008 and 2010 for Enterobacter (60% and 58%) and had a tendency of continuous growth in the period 2008-2010, from 80% to 83% and to 100% for Klebsiella. Also, the resistence was present at several strains: 70% in Enterobacter, Klebsiella over 86% to over 57% to Serratia.

Most of the strains of Pseudomonas aeruginosa were isolated from the surgical wounds of the colon; the incidence of PONI produced by his bacteria is of 10.77%. 35% of the strains showed multidrug-resistant and the carbapenem-resistant phenotype represented 25% of the

strains. The tendency of the annual incidence of bacillus Pseudomonas strains resistant to carbapenems was down from 44% to 20% in 2008-2010.

Proteus bacillus isolated exclusively from the wounds after the general surgery interventions, most of them from surgical wounds of the colon. The incidence PONI produced by Proteus was 7.69% and the isolated strains do not have brought particular problems of resistance to the common antibiotics.

The most frequently isolated of cocci was Enterococcus, which produced PONI in the cases of the general surgery interventions (especially colon surgery) and orthopedic. PONI produced by enterococci incidence was 21.02%. The multidrug-resistant was present in **75%** of the strains tested; in 2008 was isolated a strain of E.faecium vancomicin resistant (phenotype VanA), which presented resistance to other five classes of antibiotics, except the glycopeptides: aminopeniciline with IBL + carbapenems + aminoglycosides + fluoroquinolones + macrolides. It was the only strain isolated from the surgical wounds in these three years, so that, in comparison with the total number of the strains, vancomicin resistance was 2.44%.

Staphylococcus produced PONI in the case of the general, ENT and orthopedic surgeries, most of the strains isolating from the wounds from the open reduction of the fractures. The incidence of he postoperative infections produced by staphylococci was 16.92%. The methicillin resistant phenotype was present in 61.3% of strains and MLSBI phenotype in 27.58%. The annual incidence of MRS strains had an increasing tendency from 40% in 2008 to 60% in 2010. All the MRS strains showed resistance to four or five classes of antibiotics (most commonly to aminoglycosides + fluoroquinolones + macrolides and lincosamides + tetracyclines + rifampicin).

Candida produced PONI only at ENT, the incidence being 1.02%.

Study II Research on the Nosocomial Sepsis at the Operated Patients in Intensive Care

In this study, we started from the **working hypothesis (Chapter 10)** according to which from the patients who are the cases of the intensive care units, the operated patient is a separate entity, because of the state of the immun-suppression induced by the anesthesia and the operator act itself, which is added to the basic pathology that requires the hospitalization in this service. Their exposure to the bacterial flora and invasive maneuvers specific to the ATI units are added at the risk factors, being able to determine the appearance of the bacteremia. The potential risk factors for bacteremia at the operated patients must be known to implement the appropriate prophylaxis or therapy, to avoid the unjustified antibiotic usage and to avoid the prolonging hospitalization in intensive care services of the operated patients. On the other hand, the more the therapy is started later, the more difficult is the patient's recovery, so it seemed to be important to identify those clinical conditions that may alert the clinician about the risk of sepsis. **The main aim** of this study was to identify the risk factors and to assess their magnitude in the appearance of the nosocomial bacteremia and of the sepsis (BSN) at the patients who suffered surgeries, being hospitalized in the intensive care units. **The study objectives** were to evaluate the incidence of BSN, the identification of the main risk factors for the BSN at the

operated patient, the assessment of the magnitude of the risk factors in the appearance of BSN at the operated patient.

In **Chapter 11** we presented the study and witness groups and the working methodology. The study was conducted between 01.01.2005 - 31.12.2011 by following the patients hospitalized in ICU service from County Emergency Hospital from Sibiu, who during hospitalization were diagnosed with the nosocomial sepsis.

The ICU service from County Emergency Hospital from Sibiu is the largest unit with medical surgical profile in the county, having a total of 24 beds. During the seven years when the surveillance was, there have been hospitalized a total of 14,801 patients, both operated and unoperated. We studied only patients who stayed in ICU for a period of at least 48 hours, ie 4857 cases. Among the operated patients and hospitalized in ICU over 48 hours, a total of 27 were diagnosed with the nosocomial sepsis. The confirmation of the nosocomial sepsis was done by filling the specific sheet of the case of nosocomial infection by the anesthesiologist.

For comparison, we selected a **witness group** from the operated patients, hospitalized at least 48 hours in the ICU in the same period wih the cases but who did not have sepsis and at whom the concomitant presence of other infections, was not a criterion of exclusion. The control group consisted of 27 patients ("matched controls"); the main criterion of "matching" with the patients from the study group was **the diagnosis on admission, similar with the cases.**

The main criteria for the inclusion in **the group of cases** were:

a. diagnosis of nosocomial sepsis in an operated patient according to its case definition, diagnosis established by the anesthesiologist, recorded and initialed by him in the individual sheet of the case of nosocomial infection;

b. patient admitted in ICU for a period bigger than or equal to 48 hours

The exclusion criteria of the study group were:

a. length of stay in the ICU ward less than 48 hours

b. patients with pseudbacteriemia (transitory bacteremia or the superinfection of the collected sample or transported incorrectly);

c. patients with positive blood cultures for the bacteria which are the cause of an infection already present at the hospitalized in ICU

d. patients with septicemia which started within 48 hours of hospitalization.

On these criteria, we identified 27 operated patients with nosocomial sepsis, which constituted the study group.

For the 27 patient cases were noted the following variables, which were recorded on a sheet type of supervision: age, sex, date of hospitalization, date of hospitalization and discharge from ICU and the total days of hospitalization in ICU, the presence or not of the death, the presence of the antibiotic in the moment of the hospitalization at ICU, type of surgery (scheduled or emergency), the presence of anemia and the diagnosis of diabetes when the patient was admitted at ICU, the presence of ventilatory support, the duration of ventilatory support, the number of intubation during the hospitalization, the presence of the central venous catheterization, the duration of catheterization, the number of vascular catheters (CVC) during the hospitalization, the presence and duration of urinary survey, the onset time of BSN, the

concomitant presence of other localized infection at the time of hospitalization at ICU (which is not in relation with BSN) and their type.

Regarding **the witness group**, 27 patients were selected and were "matched" with other patients-cases; the inclusion criteria were as follows:

a. operated patient, hospitalized at ICU in the same time with the cases;

b. the patients with main admission diagnosis similar to that of the cases (the main criterion of "matching");

c. patients hospitalized at ICU at least 48 hours;

d. patients who had not sepsis during the hospitalization at ICU, even if they had other infections, localized (nosocomial or not).

Also in the case of the witnesses, all the variables were noted. It was clearly defined in **section 11.2.2.,** from 11.2.2.1 to 11.2.2.11.

The following chapters are detailed:

 11.2.3 Methodology of the analysis of BSN incidence

The analysis was performed by a cross-sectional study during 2005-2011, which aimed to measure the incidence of the nosocomial sepsis and the tendencies during the surveyed period, and the comparison of the results with the public data from Romania and other countries.

The incidence was defined as the number of new cases of BSN at the hospitalized and operated patients at ICU, reported to the total number of discharges from this service.

 11.2.4 The methodology of the analysis of the risk factors for BSN in the study group compared to the witness subgroup

Through a ***study of a case-witness type,*** we pursued the analysis of the potential risk factors and their impact on the nosocomial sepsis occurrence.

 11.2.5 The methodology of the data processing

The programs used for the database processing and the statistical processing are detailed in section 8.2.7. Because in this second study, the patients from both groups were "paired", we used paired statistical tests, either parametric or nonparametric: paired T student test and Wilcoxon test. The analysis of the amount of the time until the onset of the death in the operated patients, hospitalized at ICU (with or without sepsis) was performed using Kaplan-Meier survival curve.

In **Chapter 12** were recorded the results of the study on BSN.

The results of the analysis of the incidence BSN at ICU (section 12.1 and 12.2.).

The analysis was done as a whole and separately for the seven studied years.

The BSN incidence calculated by the reference to the total number of hospitalizations at least 48 hours was 0.55% (or 5.5 ‰) (table no. 4).

Table no. 4

The overall incidence of BSN in the ICU during 2005-2011

Number of patients hospitalized at least 48 hours	Number of surgical patients with BSN	The overall incidence of BSN (‰)
4857	27	**5,5‰**

The major incidence of the nosocomial sepsis was in 2005 and 2006 (table no. 5).

Table no. 5

The BSN incidence of BSN in the ICU during 2005-2011

Year	Number of surgical patients with BSN	Number of hospitalized patients	The overall incidence of BSN (%o)
2005	5	339	14,74
2006	8	521	15,35
2007	2	689	2,90
2008	2	816	2,45
2009	3	805	3,72
2010	5	839	5,95
2011	2	848	2,35

The tendency of the evolution of BSN was variable: after an initial significant decrease in the mid-range (2007-2008), followed a slight increase in 2009 and 2010, followed by a decrease again in 2011. The difference between 2006 (the year of maximum incidence) and 2007 and 2008 was statistically significant **(P = 0.0242 and p = 0.0172).**

12.2. The results of the analysis of the risk factors for BSN in the study group compared with the witness group

Through a study of case-witness type, we tried to analyze various risk factors, different possible association between the comorbidity of operated patients and the nosocomial sepsis, to enable effective intervention where possible to reduce these surgical infectious complications at the patient. We analyzed both the risk factors related to the operated and admitted at ICU patient and the risk posed by the invasive maneuvers, specific to this service.

When comparing the two groups **(section 12.2.1.)** I found that the variables for which exist statistically significant differences were: **the presence of other infections during hospitalization at ICU - P = 0.0104; the presence of anemia - P = 0.0266, the duration of the ventilatory support - P <0.0001 (fig.nr.8) and the number of re-intubation - P = 0.0034, the presence CVC P = 0.0014, the duration of the catheterization - P <0.0001 (fig.no. 9) and the number of the mounted catheters - P = 0.0001; the duration of the urinary survey P <0.0001 (fig. 10).**

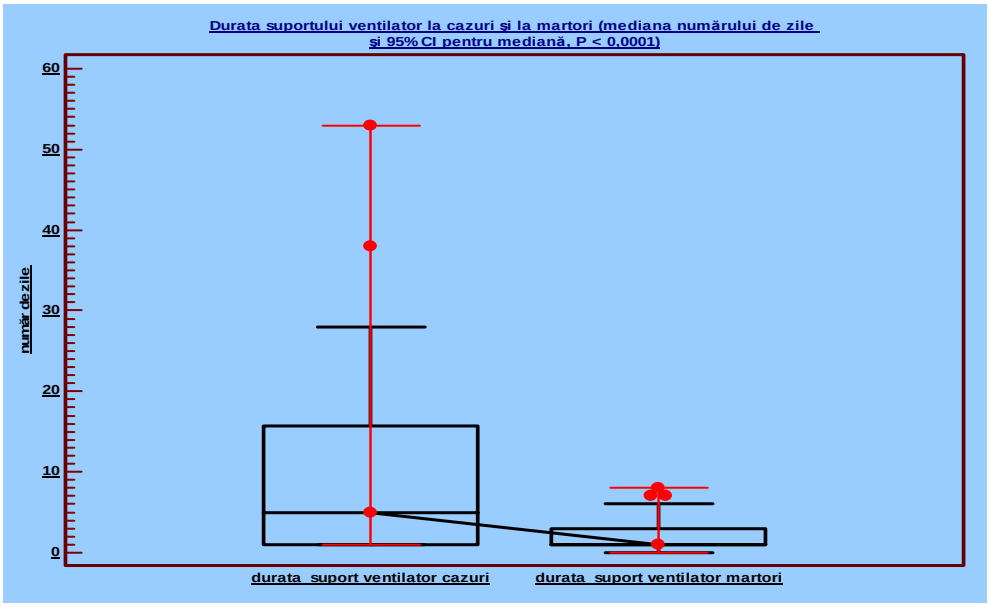


Fig. no. 8 The duration of he ventilatory support in the two groups (P <0.0001)

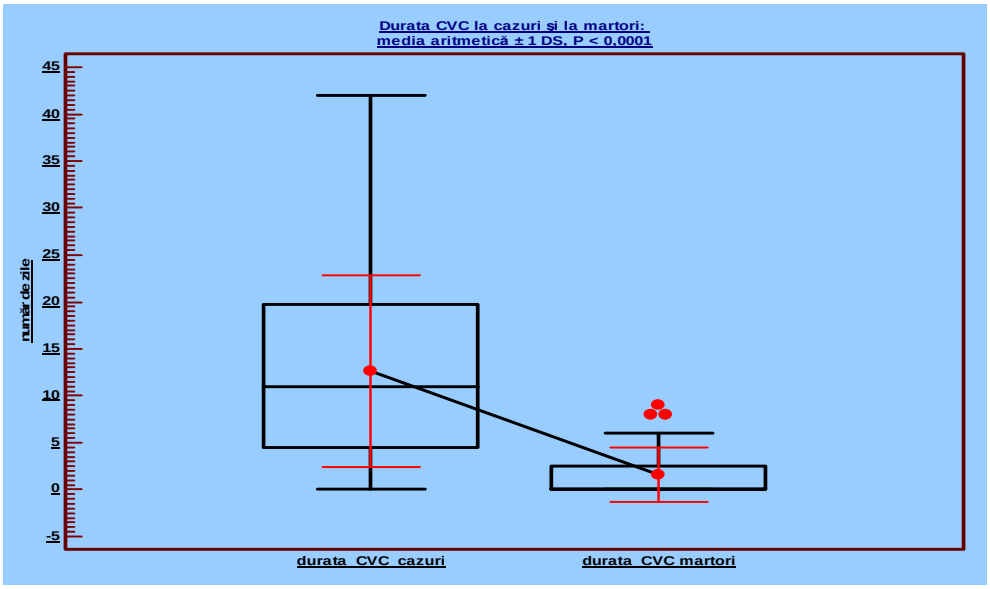


Fig. no. 9 CVC duration at the groups of the cases and witnesses, P <0.0001

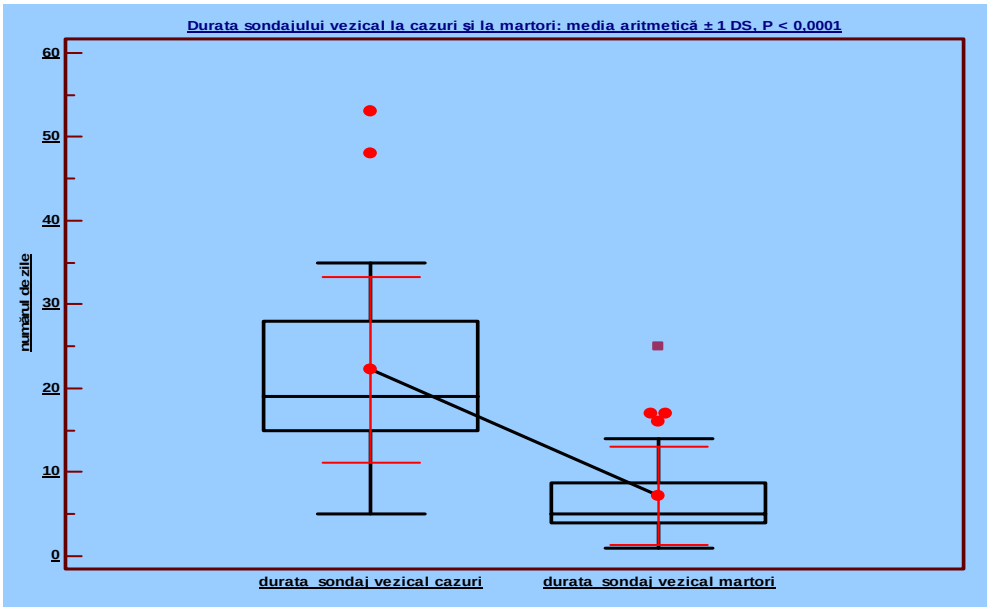


Fig. no. 10 The duration of the catheterization in the cases and witnesses groups, P <0.0001

There were no significant differences between the two groups for demographic characteristics, for the proportion of operated patients in emergency or for the proportion of the diabetic patients. The average time between the hospitalizations at ICU until the onset of BSN was about 15 days. **The proportion of deaths** among cases was significantly higher than within the witness group **(P = 0.0195). The average duration of hospitalization at ICU** at the patients cases (risk period) was significantly higher in the cases than in the witness group **(P = 0.0003).**

The main statistically significant correlations are summarized in table no. 6.

Table no.6

The main correlations between the presence of sepsis and the risk studied factors

No.	Studied correlation	Size of the lot (N)	Correlation coefficient Spearman (rho)	Level of statistical significance (P)	95% confidence interval for rho
1	**BSN- age**	54	-0,044	P=0,7488	-0,308 la 0,226
2	**BSN- age over 60 years**	54	0,148	P=0,2805	-0,124 la 0,400
3	**BSN – male gender**	54	0,040	P=0,7716	-0,230 la 0,304
4	**BSN – duration of hospitalization at risk at ICU**	54	0,458	**P=0,0009**	0,216 la 0,646
5	**BSN antibio-therapy at the hospitalization at ICU**	54	-0,041	P=0,7634	-0,306 la 0,229
6	**BSN emergency surgery**	54	0,112	P=0,4134	-0,160 la 0,369
7	**BSN anemia**	54	0,342	**P=0,0128**	0,082 la 0,559
8	**BSN diabetes**	54	0,081	P=0,5562	-0,191 la 0,341
9	**BSN other infections at the patient**	54	0,471	**P=0,0006**	0,233 la 0,656
10	**BSN duration of ventilatory support**	54	0,410	**P=0,0029**	0,159 la 0,610
11	**BSN number of intubations**	54	0,355	**P=0,0097**	0,097 la 0,569
12	**BSN central venous catheterization**	54	0,562	**P<0,0001**	0,346 la 0,721
13	**BSN duration of central venous catheterization**	54	0,661	**P<0,0001**	0,478 la 0,789
14	**BSN number CVC**	54	0,532	**P=0,0001**	0,308 la 0,700
15	**BSN duration of catheterization**	54	0,704	**P<0,0001**	0,537 la 0,817

The risk of the death among the patients with sepsis, compared with those without infectious complications was significantly (chart no. 7) and the survival curve Kaplan - Meier of the patients with BSN from the cases group and of the patients without BSN from witnesses group is like in the figure no. 11. The probability of the survival of the cases is similar with the witnesses within 5 days of hospitalization, then falling steadily for the rest of the interval of the hospitalization at ICU. By 5th day the proportion of survivors,

both the cases and the witnesses was over 90%. Subsequently, the cases, between days 5th and 15th the proportion of the survivors decreased gradually to about 68%. After day 15th (which was in the same time also the average of the onset of the BSN cases), the proportion of the survivors fell further to 52% on 19thday, then up to 41% on 23rd day.

Chart no. 7

The risk of death at hospitalized patients with the nosocomial sepsis at ICU

Patients N=54	Death	
	Attendant	Absent
Cases N=27	11	16
Witness N=27	3	24
Odds ratio = 5,5000 95 % CI = 1,3231 la 22,8627		

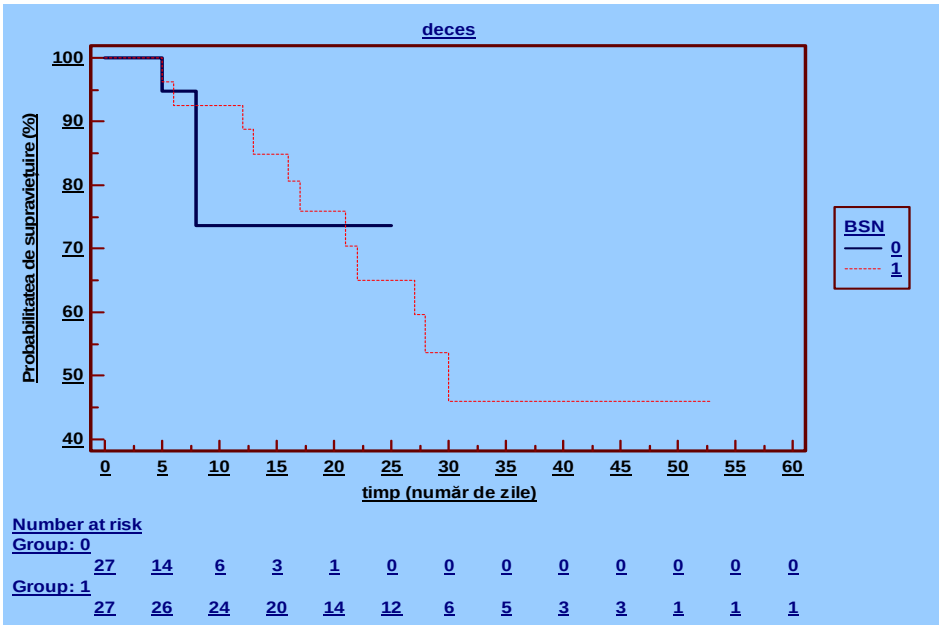


Fig. no.11 The survival curve of the operated patients with and without BSN, hospitalized at ICU

The multivariate analysis of the associations between the studied risk factors and the nosocomial sepsis (section 12.2.3.) Because, from the invasive maneuvers, the central venous catheterization was not done in all patients with BSN, firstly, we made models where we introduced this potential risk factor.

At the operated patients, hospitalized more than 48 hours at ICU and who are not central catheterised but at whom the catheterization and the ventilatory support are present, the risk of the acquiring the nosocomial sepsis was related to **the number of the days spent at ICU (P = 0 , 0322, OR = 1.16) and to the presence of the concomitant infection (P = 0.0233, OR = 8.81) and the presence of the anemia,** which tends to have statistical significance **(P = 0.0515, OR = 4 , 85).** Taking into account the duration of the invasive procedures, the risk at the patients without CVC changes: **anemia is a significant risk**

factor for the sepsis (P = 0.0389, OR = 23.65), as well as **the duration of the catheterization (P = 0.0102, OR = 2.26)** and **the age over 60 years (P = 0.0494, OR = 27.32); the duration of the ventilatory support tends to be statistically significant (P = 0.0880, OR = 1.33).** The duration of the hospitalization at ICU and other concurrent infections have no impact on the risk of BSN.

At the operated patients, hospitalized more than 48 hours at ICU, at whom the central venous catheterization, the catheterization and the ventilatory support are present, **the presence of CVC (P = 0.0158, OR = 16.1162) and the concomitant presence of the infection (P = 0, 0233, OR = 17.0657)** were significant risk factors**; the age over 60 years (P = 0.0767, OR = 5.43) and the number of days at risk at ICU (P = 0.0519, OR = 1 , 1831)** had statistically significant tendency. The same variables remain significant if the adjustment for the emergency surgeries is made.

In terms of duration, of the three types of the invasive maneuvers at operated patients who are hospitalized at ICU more than 48 hours, **the duration CVC (P = 0.0235, OR = 1.64**) and **the duration of the catheterization (P = 0.0394, OR = 1.19)** were significant risk factors for BSN; **the age over 60 years (P = 0.0711) and the presence of the concomitant infection (P = 0.0708)** tend to have statistical significance.

In terms of the number of the invasive devices, at the operated patients hospitalized more than 48 hours at ICU for the sepsis risk was significant **for the number of CVC used (P = 0.01, OR = 5.65). The number of the intubation, the presence of other concomitant infections in patients (P = 0.054) and the age over 60 years (P = 0.051)**, along with this variable, tend to be statistically significant (P = 0.067).

In terms of the impact on the risk of sepsis, on the duration or on the number of the invasive used devices, I have found that the duration of these procedures is the one that has a significant impact on the risk of the sepsis at the operated patients in intensive care **(P = 0.0317, duration CVC , OR = 1.39, P = 0.0383, duration of the ventilatory support, P = 0,0383, OR = 1.17 and the duration of the catheterization, P = 0.0002, OR = 1.25).**

In **Chapter 13**, **of the discussions**, we made a comparison between the data obtained from two researches and the existent data in the literature.

In the case of *the diabetes,* this is not only a recognized risk factor for the septic complications, but is also an important predictor of morbidity and mortality after surgery, some studies estimating that 35-50% of the patients with such complications are diabetic **(22).** The postsurgical infectious complications in diabetics may be due to the changes caused by the chronic hyperglycemia, which includes the atherosclerotic vascular disease, peripheral neuropathy and autonomic nervous system. It is therefore important for the patient the preoperative evaluation to find out unknown or uncontrolled diabetes **(23**), the determination of the glycosilated haemoglobin (HbA1c) being able to provide valuable information for the assessment of the average values of the glucose in the last 2-3 months.

On the other hand, whether or not they are diabetes, many patients, in stress pre or post operative conditions develop *perioperative hyperglycemia*. In this study we demonstrated the association between the perioperative hyperglycemia with values above

155mg/dl and the appearance of PONI. The postoperative hyperglycemia, in the early days, should be carefully monitored and treated, being known that the development of the infection depends on the way the patient's body fight in the first 48-72 hours after surgery. The mechanisms by which the perioperative hyperglycemia may facilitate the wound infection are the reduction of the vascular circulatory flow to the wound, a study demonstrating that when the non-diabetic patient ingests a dose of glucose, the dilation mechanisms which depend on the endothelium at the level of macro and micro circulation, are affected (by a mechanism similar to that seen in diabetic patients) **(24).** The second mechanism that can occur is the reduction of the cellular immunity, as chemotactic function and phagocytic function of the polymorphonuclears and of the functions of the monocytes and macrophages that have been observed in the situations of the acute hyperglycemia **(25)**. So, the hyperglycemia influences the host defense and increases the risk of the infection, both in diabetics and non diabetics after the surgery.

The perioperative blood glucose level was the most important risk factor for PONI in several studies that have evaluated different values thereof: 180 mg/dl to 12 hours postoperatively **(26),** 125 mg/dL preoperatively and 200 mg/dl after surgery **(27)**, 150-200mg/dl the perioperative period **(28),** postoperative hyperglycemia with values above 200mg/dl **(29).**

The control of the *perioperative hyperglycemias* must be therefore a goal, both in the case of the operated diabetic patient and of the non diabetic and requires the collaboration of the anesthesiologist, the surgeon and postoperative care staff.

The prolonged preoperative hospitalization predisposes the colonization of the patient with the hospital flora and the therapeutic preoperative and diagnostic procedures are all the opportunities for the contamination with this flora. A study published in 2010 showed that the prolonged hospitalization before the scheduled surgery was associated with significant infectious complications (sepsis, urinary infections, pneumonia and surgical wound infections), and with increased mortality; for the colon resection, for example, the rate of the nosocomial infections was 8.43% in patients with 0 days of preoperative hospitalization, 11.86% in 1 day, 15.79% in 2-5 days and 21.62% in those with 6 - 10 days preoperative hospitalization. Because of the infection, the costs increased from $ 13,660 to $ 25,307 **(30)**. Avoiding preoperative hospitalization which is not necessary, has the potential to reduce the postoperative infections, but must be set the strict management procedures that limit to a minimum need the preoperative hospitalization.

The prolongation of the operator specific the "T" was another significant risk factor, the explanation may be that during the extended operations there is a deeper tissue desiccation, increases the potential of the hypothermia in the patient and, last but not least, increases the time of exposure to bacteria from the wound tissues **(14)**. On the other hand, a rushed surgery may increase the risk of the intraoperative contamination or can determine an inadequate hemostasis which will require reinterventions and also increases the risk of PONI. Therefore, while "T" is a reference operator for the surgeon, so that the surgeries are

not to be prolonge unjustified, but the setting of the strict speed limits at a surger is not necessary or indicated, such an approach can be confusing.

At the level of the entire cohort of patients, before making the adjustments for NNIS risk score, we found a significant association between the age over 50 years, namely between 51 and 70 years and the emergence of PONI. There have been many studies that have attempted to explain the relationship age - PONI **(31, 32, 33, 34)**. It was argued that the factors indirectly related to age (the chronic diseases, the increased severity of the acute episodes of the diseases, the impaired immune response) are related to the increased risk for the elderly PONI **(35).**

Generally, the literature does not refer to the association between the patient *gender* and the risk of the infectious complications. There are studies that claim that men have an increased risk compared with the women to be colonized with multidrug-resistant germs such as MRSA **(36).** There can be several explanations: males are more prone to certain chronic diseases, including nephropathy in diabetes, which eventually leads to dialysis, the risk factor for the colonization with staphylococcus; the peripheral vascular disease seen in diabetics is four times more common in men, which interferes with the process of the healing of the wounds and with the prolongation of the hospitalization **(37);** men are more likely than women throughout life exposed to the invasive maneuvers such as bladder catheterization. In a study regarding PONI in the colon surgery **(38)** the presence of the infections was associated with the male gender, age, ASA score, duration of surgery and emergency procedures.

In this study we found that the association between the male sex and the infection is statistically significant only in 'healthy'patients, with no risk factors related to the surgery, so with the NNIS risk 0. To these, only the male membership and multiple intraoperative maneuvers were significant risk factors for PONI.

In this cohort of patients, the type in which *anemia* was introduced as a dichotomous variable was the only one that had a significant association with the risk of PONI. Some authors argue that maintaining a level of oxygen saturation, significantly reduces the risk of the death in patients with severe sepsis or septic shock **(39).** The mechanism is not well established, but a low concentration of haemoglobin seems to predispose to acute bacterial infection, possibly just by reducing the oxygen saturation in the situs **(40).** The surgeon should be aware of the preoperative diagnosis and, where it is possible that the intervention be delayed, to indicate its correction with iron, vitamin B12 or human erythropoietin. Mostly, the time does not permit such corrections, but preoperative knowledge can influence the subsequent management of the case. In this study, there were few cases of severe anemia, which could require allogenic red cell transfusion and the type where we have included the anemia with a value below 8.1 g / dl, it lost its statistical significance risk factor. On the other hand, the preoperative and postoperative correction of the severe anemia through transfusions is itself a risk factor to increase the postoperative morbidity and mortality, and has to be taken into account **(41, 42).**

In the second study, the incidence of BSN was 5.5 ‰, which would fall in the average area of the incidence ranges of values (2.8 ‰ - 10.3 ‰) that I met in the literature **(43, 44).**

The association of the sepsis with high mortality is common in many studies over the time **(45, 46**), reaching the rates from 41.8 to 45% **(47).**

The importance of the risk related to the invasive devices at the patient resulted in the EPIC study (European Prevalence of Infection in Intensive Care) **(48)**, study which includes data collected from over 10,000 patients. They found that 4 variables related to the invasive medical devices were independent risk factors: CVC (OR = 1.35), *the pulmonary artery catheterization* (OR = 1.20), *the catheterization* (OR = 1.41) and *the mechanical ventilation* (OR = 1.75). In another study **(49)** realized with the inclusion of over 1350 patients, there were found significant differences regarding the BSN risk according to the *duration of the central venous catheterization*: 6% by day 15th, 21% by day 30th, 52% by day 320th. The conclusion was that the risk is heterogeneous and increases with the duration of the catheterization.

Even if some risk factors cannot be influenced (age) or are difficult to be changed (duration of hospitalization at ICU, the presence of the anemia and the presence of other infections at the hospitalization at ICU), the risk factors regarding the invasive devices (CVC, catheterism, intubation and mechanical ventilation) may be influenced in each patient by creating and abiding a practice guidelines which state the need and the recommended duration of these maneuvers, with their immediate removal when the patient outcomes permit.

To conclude, in this chapter we centralized in the Table no. 8 the associations with the statistical significance between the presence of the infectious complications and the risk factors investigated in the two studies included in this paper.

Table no. 8

Statistically significant association between the postoperative infectious complications and the risk factors studied in the surgical wards and intensive care

No.	Studied variables	P
Postoperative nosocomial infections		
Combinations obtained without adjusting for NNIS risk score		
1.	**PONI - emergency surgery**	**P=0,0125**
2.	**PONI - diabetes**	**P=0,0119**
3.	**PONI - wound contamination class**	**P=0,0001**
4.	**PONI - ASA score**	**P=0,0168**
5.	**PONI - prolonged postoperative hospitalized atICU**	**P=0,0022**
6.	**PONI – duration of surgery**	**P=0,0174**
7.	**PONI - preoperative hospital duration**	**P=0,0514***
8.	**PONI - ICU hospitalization over 48 hours**	**P=0,0000**
9.	**PONI - hyperglycemia over 155mg/dl**	**P=0,0163**
10.	**PONI - over time operator "T"**	**P=0,0072**

11.	PONI - preoperative hospitalization over 48 hours	P=0,0276
12.	PONI - patients aged between 51 to 70 years	P=0,0201
Combinations obtained by adjusting the NNIS risk score		
13.	PONI - males (with adjustment for NNIS risk score 0)	P=0,0221
14.	PONI - multiple procedures performed during surgery (the NNIS risk adjustment score 0)	P=0,0156
15.	PONI - operations performed in emergency (adjusting for NNIS risk score 1)	P=0,0027
16.	PONI - longer duration of postoperative hospitalization at ICU (with adjustment for NNIS risk score 1)	P=0,0248
17.	PONI - prolonged preoperative hospitalization (with adjustment for NNIS risk score 1)	P=0,0361
18.	PONI - patients from the age group 31-50 (with adjustment for NNIS risk score 1)	P=0,09*
19.	PONI - preoperative anemia (adjusting for NNIS risk score 2/3)	P=0,0132
20.	PONI - diabetes (with adjustment of NNIS risk score 2/3)	P=0,0188
21.	PONI - emergency surgery (the NNIS risk adjustment score 2/3)	P=0,0098
22.	PONI - prolonged hospitalization at ICU (with adjustment for NNIS risk score 2/3)	P=0,0364
23.	PONI - perioperative hyperglycemia with values above 155mg/dl (adjusting for NNIS risk score 2/3)	P=0,0116
24.	PONI - patients aged between 51 and 70 years (adjusting for NNIS risk score 2/3)	P=0,0146
25.	PONI - hospitalization at ICU more than 3 days (with adjustment for NNIS risk score 2/3 and scheduled operations)	P=0,0256
Nosocomial sepsis in operated patients		
Associations at the patients without central vascular catheterism		
26.	BSN - number of days spent at risk at ICU	P=0,0322
27.	BSN - presence of concomitant infections	P=0,0233
28.	BSN – anemia (with adjustment for duration of invasive maneuvers)	P=0,0389
29.	BSN - duration of the catheterism	P=0,0102
30.	BSN - age over 60 years	P=0,0494
31.	BSN – duration of ventilatory support	P=0,0880*
Associations at the patients with central vascular cathterism		
32.	BSN – CVC presence	P=0,0158
33.	BSN - presence of concomitant infections	P=0,0233
34.	BSN – age over 60 years	P=0,0767*
35.	BSN - number of days at risk at ICU	P=0,0519*
37.	BSN – CVC duration	P=0,0235
38.	BSN – duration of the catheterism	P=0,0394
39.	BSN - number of CVC used	P=0,0125
40.	BSN - number of intubations	P=0,067*
Invasive devices impact assessment on the risk of BSN		

41.	**BSN - CVC duration**	**P=0,0317**
42.	**BSN - duration of ventilatory support**	**P=0,0383**
43.	**BSN – duration of the urinary catheterisation**	**P=0,0002**

** Statistically significant trend*

Chapter 14 Conclusions

1. The overall incidence of PONI in 2008-2010 in general surgery wards, orthopedics and ENT was 2.56%.

2. In general surgery, *the colon surgery* was the category of the surgery that had the highest rate of PONI incidence, with values of 10.91%. *The stomach surgery* (9.52%) and of *the rectum* (8.77%) occupied the second and third places as incidence.

3. In orthopedic surgery, the incidence of the total hip arthroplasty was 1.81% and 3.15% of the hip hemiarthroplasty.

4. In ENT surgery, PONI incidence was 2.51%.

5. **The emergency surgery** is a moderate risk factor at the operated patient for acquiring PONI: OR = 1.6992, 95% CI = 1.0313 to 2.7996.

6. **The risk of the death is significantly higher** among the patients with PONI than among those without infection **(OR = 4.4107).**

7. The calculation of the infection NNIS risk index showed that there is a significant risk of infection for those with **higher NNIS index, 2 and 3 (OR = 2.9520, OR = 5.9048** respectively).

8. The analysis of the risk factors for the acquisition of PONI without the adjusting for NNIS risk index showed that the significant risk factors in the postoperative infectious complications were **the emergency surgeries, the presence of the diabetes diagnosis, the wound contamination class, the ASA score, the prolonged postoperative hospitalization at ICU and the duration of the surgery (P = 0.0174, OR = 1.0050).**

9. The patients **aged between 51 and 70 years**, without adjusting for NNIS risk index had a significant risk for **PONI (P = 0.0201, OR = 1.7018),** at this group of patients, the highest risk being **the prolongation of the hospitalization over 48 hours, followed by the emergency character of the surgery, by the hyperglycemia over 155mg/dl, by the over operator time "T", by the wound contamination class, by the preoperative hospitalization over 48 hours and by the association of the comorbidities – ASA score.**

10. The analysis of the risk factors after the adjusting for NNIS risk score showed that **the male sex and the multiple procedures performed during the surgery** were the significant risk factors for the acquisition of PONI at the patients with **NNIS risk 0.**

11. At the patients with **NNIS risk 1,** significant risk factors for the acquisition of PONI were **the emergency surgieries, the long postoperative hospitalization at ICU and he prolonged preoperative hospitalization.**

12. In patients with **NNIS risk scores 2 and 3, the presence of the preoperative anemia, the diabetes diagnosis of the patient, the surgical emergency and the prolonged ICU hospitalization** were the significant risk factors for the acquisition of PONI. If at the patients wih NNIS risk scores 2 and 3, the adjusting for the *established surgeries* is made, then the significant risk factors for the appearance of the perioperative infectious complications are: **the perioperative hyperglycemia over 155mg/dl, the age between 51 and 70 years and the hospitalization at ICU more than 3 days.**

13. The PONI etiology was dominated by the bacteria, from the total of 260 microbial isolated strains representing 70%, 29.23% cocci and fungi 0.77%. Among the most common bacteria, E. coli was isolated (19.23%) and Enterococcus cocci (15.77%). The situation of the multi-resistant bacterial strains isolated from the surgical wounds is worrying.

14. **The overall incidence of the nosocomial sepsis at the surgical patients** hospitalized at ICU in a period of seven years (2005-2011) was 5.5 ‰. The average time between the hospitalizations at ICU until the onset of BSN was approximately 15 days.

15. **There is** a significant risk of the death among the patients with the nosocomial sepsis **(OR = 5.5, 95%).**

16. At the operated patients, hospitalized at ICU more than 48 hours and who are not central vascular catherized, the risk of the acquiring the nosocomial sepsis is related to **the number of the days spent at risk at ICU, the presence of the concomitant infections and the presence of the anemia,** which tends to have statistical significance **(P = 0.0515, OR = 4.85).** If we take into account ***the duration*** of the invasive procedures, the risk at the patients without CVC changes: **anemia becomes a significant risk factor for the sepsis, as well as the duration of the catheterization and the age over 60 years; the duration of the ventilatory support** tends to be statistically significant **(P = 0.0880, OR = 1.33).**

17. At the operated patients, hospitalized at ICU more than 48 hours and whom the central venous catheterization was present, **the CVC presence and the presence of the concomitant infections** were significant risk factors. If we analyse ***the duration of the invasive maneuvers*** at the operated patients hospitalized at ICU over 48 hours, **the CVC duration and the duration of the catherization**) were the significant risk factors for BSN; **the age over 60 years (P = 0.0711) and the presence of the concomitant infections (P = 0.0708)** tend to have statistical significance. Adjusting the **number of the invasive devices** at the patients hospitalized at ICU more than 48 hours, the risk for the sepsis was significant for **the number of he used CVC** and together with this variable **the number of the intubation (P = 0.067), the presence of other infections concomitant at the patient (P = 0.054) and the age over 60 years (P = 0.051)** tend to have statistically significance,.

18. **The duration** of the maintenance of the invasive medical devices is one that has a significant impact on the risk of the sepsis at the patients operated in the intensive care (**CVC duration P = 0.0317, OR = 1.39, P = 0.0383 the duration of the ventilatory support, OR = 1.17 and the duration of the urinary catheterization P = 0.0002, OR = 1.25**).

Chapter 15 Program for the Prevention of the Postoperative Infectious Complications

Designing of such a program and its measures should focus on three areas: measures during the preoperative period, intraoperative measures and postoperative measures.

I. MEASURES OF PROPHYLAXIS OF THE INFECTIOUS COMPLICATIONS DURING THE PREOPERATIVE PERIOD

A. **Preoperative measures for the patient**

1.1. The identification of any developing infection, regardless of type, their location and extension and their treatment until healed (the collaboration with the doctor).

1.2. The preoperative blood glucose level control is a goal, both in patients with diabetes and those without the disease, in order to maintain it below 155mg/dl, through the introduction of the preoperative screening of the glucose as part of the pre-anesthetic consultation and its quickly control, monitored by the anesthesiologist. At the diabetic patient, knowing the level of the glucose at time must be done by the completing the test with the determination of the glycosilated haemoglobin, HbA1c.

1.3. At the patients with anemia, if the intervention is delayed, it is desirable the correction of the anemia (the collaboration with the internist). The severe anemias, which have the indication of the transfusion, should be carefully evaluated and monitored, taking into account the risks of the blood transfusion itself.

1.4. Antibiotic prophylaxis: targeted where needed (Annex 6), adapted to the etiologic spectrum, administered in doses so that the bactericidal concentration reach the tissue before the time of the incision. The recommended way of the administration is parenteral, in doses close to the therapeutical doses. The intraoperative repetition of the doses is shown where the duration of the surgery is long, depending on the half life of the antibiotic, to maintain an adequate level throughout the surgery.

2. Preoperative measures related to the hospitalization

2.1. The reduction of the time of the preoperative hospitalization while respecting a time to allow an appropriate preoperative preparation of the patient. In the absence of other complications, a preoperative hospitalization within 24-48 hours should accomplish it.

2.2. The proper preparation of the room where the patient is hospitalized, with emphasis on the disinfection and the quality of the bed linen.

II. THE INTRAOPERATIVE MEASURES OF THE PREVENTION OF THE INFECTIOUS COMPLICATIONS

1. Intraoperative measures related to the surgical room

1.1. The abiding of the protocols regarding the disinfection of the surfaces and of air in the surgical room, the protocols which are structured in three parts: before surgery, between surgeries and after the working hours.

1.2. The sterilization of the instruments according to the manufacturer's recommendations, the guidelines and the law.

1.3. Limiting the number of surgical team at the strictly necessary persons.

1.4. Keeping the doors closed during the surgery.

2. Intraoperative technical measures related to the surgery

2.1. Taking into account the aseptic techniques when installing CVC, the peripheral catheters or the spinal catheter for the anesthesia by the team of the anesthesiologists.

2.2. The improvement of the surgical technique, with gentle tissue handling to minimize the tissue devitalisation, the achievement and the maintenance of an efficient haemostasis, cleaning, eradication of the necrotic areas of the surgical wound.

2.3. Knowing the time "T"-specific to the interventions; taking it into account reduces the risk of the infection, but it should not be a priority against the quality of the surgery act.

III. POSTOPERATIVE MEASURES OF THE PREVENTION OF THE INFECTIOUS COMPLICATIONS

1. Postoperative wound care

1.1. Taking into account the aseptic technique when dressing the wound

1.2. The antiseptic wash of the hands before handling the dressing

1.3. The frequency of the dressing change or how long must be the period of the covering of the incision with sterile dressings

2. The postoperative measures related to the patient

2.1. Keeping on monitoring for another 48 hours of the postoperative blood glucose and its regulation below 155mg/dl. The necessity of this monitoring is seen to the staff from the ward where the patient is hospitalized postoperatively.

2.2. Writing the duration of surgery and the wound contamination class in the chart as soon as possible after the surgery; these data, along with the preoperative ASA score set by the anesthesiologist are useful to calculate the NNIS score of the patient; a patient with high score 2 or 3 requires a careful monitoring to capture a possible wound infection. Once classified the NNIS risk class, the surgeon may take into account any of the following parameters which can constitute in the risk independent infectious factors for the patient:

 for the patients with **NNIS score 0**: the male gender; the performance of the multiple procedures during the surgery.

 for the patients with **NNIS score 1**: the long preoperative hospitalization; the prolonged duration of the postoperative hospitalization at ICU; the emergency performed surgeries.

 for the patients with NNIS scores 2 and 3: the anemic syndrome; the diabetes; the perioperative hyperglycemia over 155 mg/dl; the prolonged hospitalization at ICU over 3 days; the age between 51 and 70 years; the emergency performed surgeries.

2.3. Patient and family education on wound care.

3. Postoperative measures related to the hospital

3.1. At the patients requiring postoperative hospitalization at ICU, shorten at the minimum period of the hospitalization, taking into account that the hospitalization over 48-72 hours at ICU are at risk for the development of the infectious complications.

3.2. The operated patients, hospitalized at ICU, at who the central venous catheterization is required: installing CVC according to the aseptic technique (the sterile protective equipment, the isolation of the incision place with sterile field, the surgical disinfection of hands); the sterile dressing in the place of the insertion and change it weekly; the daily monitoring of the catheter insertion place; there are prohibited the topical ointment at the place of the catheter insertion; the removal of the CVC if the inflammatory signs or the purulent discharge appear at the place of the insertion; **the immediate removal of the CVC, if it is no longer necessary after use.**

3.3. The operated patients, hospitalized at ICU at who it is necessary *the urinary catheterisation*: assembly the catheter by the trained personnel, according to the aseptic conditions (the antiseptic washing hands, the cleaning of the genital area and of the external urethral meatus); the usage of the wells with the small diameter; setting firmly the catheter; the usage of a closed drainage system; the replacement of the sterile collection system with another one, if it is necessary; he monitoring of the system to avoid the obstacles regarding the urine flow; it is not necessary to change the catheters if the infectious signs lack; **the immediate removal of the urinary catheter if it is no longer necessary after use**.

3.4. The operated patients, hospitalized at ICU at who it is required *the ventilatory support*: the oro-tracheal intubation is preferred to the naso-tracheal one; the fans circuits, humidifiers, etc must be sterile when the patient is connected; the contaminated condensate from the ventilator circuit must be emptied carefully and must be avoided its penetration into the endo-tracheal tube or into the nebulisation lines; if it is possible, the continuous suction of the subglotical secretions; the tracheal aspiration is done with sterile catheter and of single use; **the reduction of the duration of the intubation and of the mechanical ventilation.**

4. Surveillance

The PONI incidence should be calculated periodically, both as a global indicator and for the categories of surgery and stratified by NNIS index of the cases; the dissemination of the results should be made to the surgeons at intervals not longer than one month. Thus, on the one hand, the surgeon can always know which are the types of the interventions on which the effort has to be focused on to prevent the infectious complications, and on the other hand, there can be made the comparisons of the rates between the hospitals of the same type from the country and from the world. The identification of the cases in a combined prospective and retrospective manner, have to be completed with the supervision of the patients within the first month after their discharge to identify those PONI with late-onset, at home.

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