MEDICAL UNIVERSITY - PLOVDIV

Department of cardiovascular surgery

Cardiac surgery clinic

Dr. Hristo Angelov Stoev

WOUND INFECTIONS AFTER OPEN HEART SURGERY

Abstract

of a dissertation

for acquiring the educational and scientific degree “Doctor”

Scientific specialty: Cardiovascular surgery

Scientific supervisor: Prof. Zaprin Vazhev, PhD

Plovdiv, 2021

The dissertation contains 207 pages. It is illustrated with 36 tables, 35 diagrams and 55. The bibliography includes 360 sources, of which 8 are in Cyrillic and 352 in Latin.

The dissertation was discussed and accepted at the extended department council at the Department of cardiovascular surgery, Medical University - Plovdiv (Protocol № 131/28.01.2021).
The public defense of the dissertation will be held on ..... at ....., in ..... auditorium of the Auditorium Complex of MU-Plovdiv, 15 A. Vasil Aprilov Blvd.

Scientific jury:
1. Prof. Boris Sakakushev, PhD
2. Prof. Rosen Dimov, PhD
3. Prof. Plamen Panayotov, PhD
4. Prof. Mario Stankev, DMSc
5. Prof. Aleksandar Chervenyakov, DMSc

Interim members:
1. Prof. Ivan Dechev, PhD
2. Ass. prof. Dimitar Petkov, PhD

The materials from the dissertation are available at the Department of cardiovascular surgery, Medical University - Plovdiv, 66 Peshtersko shose Blvd. and are published on the website of MU - Plovdiv.

Note: the numbers of the tables and figures in the abstract do not correspond to those in the dissertation.

Table of contents

Abbreviations and acronyms

DIS - Deep infections of the sternum
SCF - Sternocutaneous fistula
CABG - coronary artery bypass grafting
VAT - Vacuum-assisted therapy
COPD - Chronic obstructive pulmonary disease
AB - Antibiotic
ECC - Extracorporeal circulation**; CPB -** cardiopulmonary bypass
EF - Ejection fraction
MIC - Minimum inhibitory concentration
CDC - Center for Disease Control
MRSA - Methicillin-resistant Staphylococcus aureus
VRE - Vancomycin-Resistant Enterococci
ESBL - Extended-spectrum beta-lactamase
SIRS - Systemic inflammatory response syndrome
MODS - Multiple organ dysfunction syndrome
BMI - Body Mass Index
ITA - Internal thoracic artery
BITA - Bilateral internal mammary artery grafting
IABP - Intra-aortic balloon pump
CVVHDF - Continuous Veno-Venous Hemodiafiltration
CoNS - Coagulase-negative staphylococci
MRSE - Methicillin-resistant S. epidermidis
EuroSCORE - European Cardiac Operative Risk Evaluation System
STS - Society of Thoracic Surgeons
CRP - C-reactive protein
PCT - Procalcitonin
ProBNP - B-type natriuretic peptide

1. Introduction

Deep wound infections represent a serious complication after open heart surgery and are directly related to patient survival in both the short and long term. They are associated with extended hospital stay and the use of expensive medicines and consumables, which leads to increased financial costs.

Despite prophylaxis, their manifestation remains significant - from 0.5% to 6.8%, and the associated in-hospital mortality varies from 7% to 35%. Late infections, which can lead to the development of chronic mediastinitis and sternocutaneous fistulas, are less common, but often present as a complex surgical problem involving several elements: rehospitalizations, long-term antibiotic treatment, and recurrent infections. The latter severely reduce the quality of life of the patients who have undergone heart surgery. Over the last two decades, more effective treatment methods have been introduced, which have significantly reduced mortality - especially after the introduction of negative pressure wound therapy or the so-called vacuum assisted therapy (VAT).

Median sternotomy remains the standard surgical approach in cardiac surgery, despite the growing popularity of minimally invasive approaches. Median sternotomy has many advantages: it is fast to perform and provides wide access to almost all mediastinal structures. The main disadvantage of total median sternotomy is the risk of chest instability, superficial and deep wound infections (mediastinitis), sternocutaneous fistulas.

The nomenclature and the definition of chest wound infections are not yet standardized. Post-sternotomy wound infection, poststernotomy mediastinitis, and profound chest wound infection are used to denote infections involving the sternum and mediastinal structures. However, it is important to distinguish between superficial and deep wound infections. The first - with a frequency of 0.5 to 8% according to the literature, include only the layers between the skin and the sternal fascia, leaving the sternum intact. Deep wound infections involving the sternum are less common. Their frequency depends on the classification used and varies between 0.4% and 5%, and they lead to higher in-hospital mortality. The problem of deep wound infections is becoming increasingly important for several reasons:

- The number of cardiac surgery centers and catheterization laboratories in Bulgaria is constantly increasing;
- Much of the domain of cardiac surgeons has already been "taken over" by interventional cardiologists, which means that more severely disabled patients, those with decompensated heart failure and ejection fraction (EF) below 35%, are admitted to cardiac surgery clinics, patients on dual antiplatelet therapy (with increased risk of postoperative hemorrhage and chest re-exploitation), elderly patients with limited physical capacity.

That dramatically increases the likelihood of developing superficial and deep wound infections;

- The number of reoperated patients is increasing, which is currently over 10% in most centers.

There is currently no standardized regimen for the treatment of wound infections after open heart surgery and there are no developed standardized prophylactic programs - microbiological analysis, detection of predictive biomarkers, as well as surgical techniques to reduce the occurrence of these life-threatening complications. The present dissertation aims to present the epidemiological and demographic data of patients developing wound complications, to propose surgical techniques for prevention and treatment, to present presumptive predictive biomarkers for the development of infections, to present the microbiological spectrum of the causes of these complications. The latter is extremely important for the correct choice of antibiotic (AB) prophylaxis, the time for the application of AB preoperatively and the duration of AB treatment in the postoperative period. Last but not least, the aim of the present dissertation is to present the main measures for observance of asepsis and antiseptics not only in the operating room, but also in the intensive care unit and the hospital.

2. Objective and tasks of the study

2.1. Objective of the study

To study the frequency, microbiological agents and risk factors for the development of wound infections after open heart surgery and to assess the role of predictive biomarkers, innovative preventive measures and treatment outcomes, including hospital stay and mortality.

2.2. Tasks of the study

1. To analyze the microbiological agents by evaluating the microbiological results of wound secretions and the predominant bacterial flora in the clinic, in order to optimize intravenous antibiotic prophylaxis;
2. To calculate the frequency of deep and superficial wound infections and sternocutaneous fistulas in a large cardiac surgery center and to determine the risk factors for their development;
3. To assess and analyze the risk factors for the development of post-surgical wound infections and to propose measures to limit contamination;
4. To compare the results of the treatment of deep wound infections (mediastinitis) after open heart surgery using different methods of treatment - vacuum-assisted therapy with subsequent refixation; refixation with irrigation of antiseptic solution; omentoplasty;
5. To assess the predictive value of certain biomarkers for the development of wound infections and septic conditions;
6. To develop and evaluate a new technique for local antibiotic prophylaxis in cardiac surgery;
7. To propose a comprehensive protocol for prevention and comprehensive treatment of poststernotomy wound infections.

3. Materials and methods

The clinical studies are conducted in the Clinic of cardiac surgery (founded in October, 2002) at the University Hospital "St. Georgi ”- Plovdiv, which is part of the Department of cardiovascular surgery at the Medical University - Plovdiv. The institution is the third largest in Bulgaria, which is the main prerequisite for analyzing a large number of patients and for applying various diagnostic methods and treatment techniques. For the period October 2002 to June 2019, 10 307 open heart surgeries with total median sternotomy are performed in the clinic, 10 100 of which were with extracorporeal circulation.

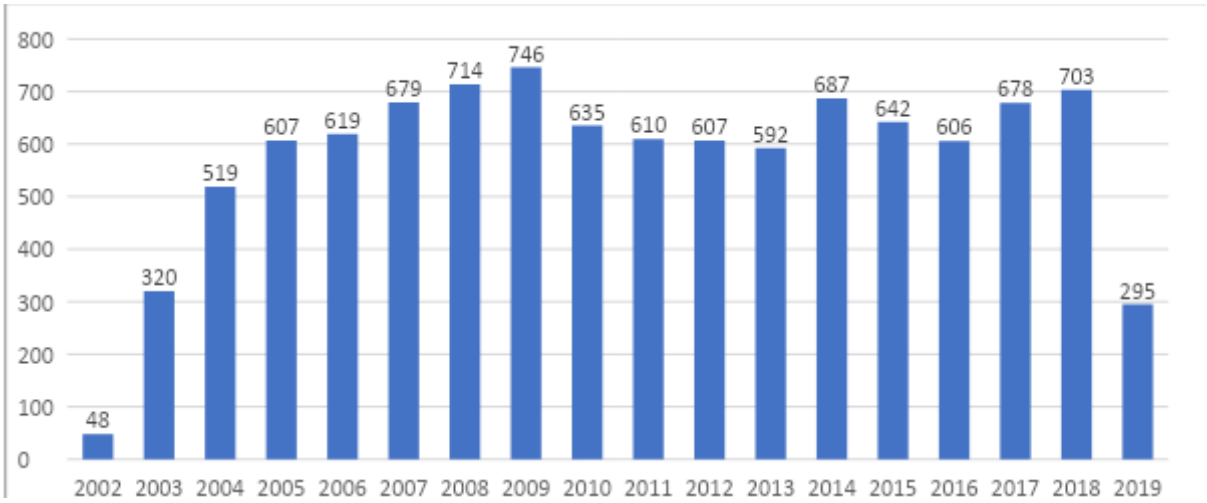


Diagram 1: *Open heart operations by years*

One of the aims of the present study is to determine the incidence of surgical site infections over a 17 - year period in 10307 patients after cardiac surgery with total median sternotomy (Table 1). Postoperative infections are classified according to the modified Friberg classification based on CDC recommendations. According to the time of diagnosis, they are classified according to the classification proposed by Pairolero and Arnold.

Table 1: *Wound complications after open heart surgery by years*

Year	**Total number of operated**	**Deep wound infections**		**Superficial wound infections**		**Sterno-cutaneous fistulas**	
2002	48	0	0%	1	2.08%	0	0%
2003	320	2	0.62%	4	1.25%	0	0%
2004	519	3	0.54%	4	0.54%	2	0.38%
2005	607	4	0.65%	20	3.29%	3	0.49%
2006	619	5	0.80%	17	2.74%	2	0.32%
2007	679	5	0.73%	19	2.79%	1	0.14%

2008	714	6	0.84%	48	6.72%	3	0.42%
2009	746	8	1.07%	61	18.17%	2	0.27%
2010	635	7	1.10%	38	5.98%	2	0.31%
2011	610	9	1.48%	42	6.88%	3	0.49%
2012	607	10	1.64%	54	8.90 %	2	0.32%
2013	592	14	2.36%	59	9.91%	3	0.50%
2014	687	13	1.89%	48	6.97%	3	0.43%
2015	642	14	2.18%	59	9, 91%	1	0.16%
2016	606	15	2.47%	69	11.38%	4	0.66%
2017	678	19	2.80%	61	8.99%	3	0.44%
2018	703	9	1.28%	29	4 , 12%	1	0.14%
2019	295	3	1.01%	4	1.35%	0	0%
Total:	10307	146	1.42%	637	6.18%	35	0.34

From the analysis of data in recent years, especially 2014, 2015, 2016 and 2017, an increase in the incidence of superficial and deep wound infections was found. This necessitated the study of risk factors for their development, search for predictive biomarkers for their early diagnosis at the subclinical level, application of innovative methods for prevention (surgical technique, AB prophylaxis and optimized AB therapy) and their actual implementation in the clinical practice. Patients with deep wound infections (DIS) were analyzed retrospectively, as they represent a very serious problem in cardiac surgery due to the high associated mortality and high financial costs. Different methods for treating these diseases in terms of survival, treatment success, hospital stay, and complications were compared. Therefore, the dissertation is divided into several main sections. For the period July 2017 - February 2018, 137 coronary patients were examined in order to analyze the prognostic value of a panel of laboratory biomarkers proposed by our institution and to analyze the microbiological flora in the clinic. In 2018, a modified surgical approach was applied to 300 patients in the fixation of the sternum and the closure of the surgical wound and the achieved results were analyzed. All this logically led to the introduction of a comprehensive algorithm (protocol) for the prevention and treatment of wound infections from the patient's admission to the clinic until the 3rd month after surgery (rehabilitation program).

3.1. Methods used according to the study plan

The following methods were used to collect the primary statistical information:

1. Operative methods

The applied operative techniques in the treatment of superficial wound infections, sternocutaneus fistulas (SCF) and DIS and the method of chest closure proposed as a prophylactic measure for the occurrence of poststernotomy infections, used in the performance of the assigned tasks are discussed in detail in the relevant sections.

1. Imaging techniques

In all patients, transthoracic echocardiography is a routine examination. Prior to the operation, chest X-rays and CT scans must be performed in all patients, regardless of whether emergency or planned intervention is forthcoming. In emergency patients, radiography is performed at the patient's bedside.

1. Laboratory and biochemical studies

Reagents and a multiparametric immunoassayer Mini VIDAS (bioMérieux, France) were used to study the proposed predictive biomarkers - troponin, PCT, pro-BNP, C-reactive protein and high-sensitive C-reactive protein.

1. Microbiological tests

Microbiological samples were taken from the wound in all patients for culture. This is achieved by means of a sterile dry swab with a viscous tip, a plastic handle and a solid Amies transport medium that comes into contact with the wound surface. The data for the microbiological isolates and AB sensitivity were processed in the Laboratory of Microbiology at the University Hospital “St. Georgi” – Plovdiv.

1. Statistical processing of the information obtained during the examination of the clinical material

Based on the main purpose and objectives of the study, as well as the volume, type and distribution of data in the study, the following statistical methods were used:

1. Descriptive statistical methods

• Quantitative metrics will be presented with the main measures of the central trend, statistical dissipation and confidence interval (mean ± SD, SE, 95% CI);

• Qualitative, unmetered values will be represented by absolute frequencies, relative proportions and standard error (no.,%, Sp);

2. Parametric and non-parametric methods

• When testing the hypotheses for insignificant (random) influence of a given factor, the Fisher's exact test for quadruple tables and the criterion for multiple tables will be used;

- Student's t-test will be used to test hypotheses for the presence of a statistically significant difference between two independent samples with studied quantitative, normally distributed indicators; when comparing quantitative values in independent samples with a distribution different from the normal one - Mann-Whitney test.
- Student's paired-samples t-test will be used to test hypotheses for the presence of a statistically significant difference between two dependent samples with studied quantitative, normally distributed indicators; when comparing quantitative values in dependent samples with a distribution different from the normal - Wilcoxon test.
- For comparison of quantitatively measurable normally distributed indicators in more than two groups - analysis of variance (One-way ANOVA); when comparing more than 2 independent samples with a distribution of data other than normal - Kruskal-Wallis test.
- ROC-curve for analysis and evaluation of the predictive value of the analyzed biomarkers; The significance level of the null hypothesis was $P < 0.05$. Statistical data processing was performed using the software product SPSS v.17. 3. Graphic methods - for visual graphical presentation of the results MicroSoft Excel 2010 was used.

4. Conduction of the study and results

4.1. Analysis of the microbiological flora in the Cardiac surgery clinic

Due to the increase in the incidence of superficial and deep wound infections, we made a retrospective analysis of the isolated microbiological flora in the clinic and AB resistance and compared the results for 2011, 2016, 2017 and 2018. DIS is 1.48%, 2.47%, 2.80% and 1.28%, respectively, superficial wound infections 6.88%, 11.38%, 8.99% and 4.12%, respectively. The study aims to improve the choice of AB for both prevention and treatment. The data are from the Laboratory of Microbiology at the University Hospital "St. Georgi" – Plovdiv. The microorganisms that are isolated are from wound, nasopharynx, tracheal samples, blood cultures, urocultures, venous and urethral catheters and implants.

Of the 234 isolates for the period January - December 2011, Gram (-) microorganisms predominate - 68.38%. The most commonly isolated species are respectively: Acinetobacter baumanii 46 (20.66%), E.coli 41 (17.52%), Klebsiella spp. 28 (11.96%), followed by Ps. Aeruginosa 23 (9.83%), Serratia spp. 17 (7.26%). Problem-resistant are the polyresistant A. baumanii species, in which the resistance is 91% for Meropenem, 80% for Imipenem, 97% for Cefoperazone/sulbactam, 89% for Ciprofloxacin. Compared to 2010, the percentage of producing broad-spectrum β-lactamase strains increased for E. coli from 30% to 50%, respectively, and for Klebsiella spp. from 12% to 20%, which determines the higher resistance to cephalosporins III generation. In 2011, compared to 2010, the number of isolated S. aureus and CoNS was higher. MRSA types are 19% in 2011 against 43% in 2010, while in methicillin-resistant CoNS the percentage increases from 43% (2010) to 50% (2011). In Enterococcus spp. the high degree of gentamicin resistance remains unchanged - 65% for 2010 and 66% for 2011. No VRE registered.

Isolates in 2016 (421) were 94 (12.80%) more than in 2015 (328). Gram (+) microorganisms predominate - 269 out of a total of 421. The leading isolated microorganism is E. coli - 78, which is a 2-fold increase compared to 2015. The percentage of methicillin-resistant CoNS is preserved - 71%. The trend of increasing the number of Acinetobacter spp. isolates continues, as their sensitivity to Colistin is 100%. The isolation percentage of Kl. Pneumoniae remains the same as in 2015, but ESBL (+) increased from 84% to 92%. The susceptibility of isolates to Imipenem and Meropenem continues to decrease (from 98% in 2015 to 96% in 2016). The number of Enterococcus spp. - 40, compared to 26 for 2015. 1 VRE (E. faecium) isolate is registered. The number of S. aureus isolates is also increasing - from 14 isolates (2015) to 26 (2016). The number of isolates of Enterobacter spp. persists, but the reduced sensitivity to Meropenem is impressive - from 100 to 94% compared to the previous year.

The number of isolated Pseudomonas spp. has decreased from 36 to 22, with a reduction in sensitivity to Imipenem from 83% to 72%.

In 2017, the number of isolated microorganisms was 311, with Gram (-) bacteria predominating. Leading microorganisms are E. coli and A. baumanii, followed by Klebsiella spp. The number of isolated E. coli is 45, which shows a significant decrease compared to the previous year. The percentage of isolated A. baumanii is maintained. Colistin - a resistant strain was isolated. Meropenem resistance is 100%. The number of Klebsiella spp. e 41. In Enterobacter there is an increase in the percentage of isolation, while Enterococcus spp. decreased in 2017. The number of S. aureus isolates was maintained and a slight increase was observed in CoNS.

In 2018, the isolates were 263, which is 75 - less than the previous year. There is a tendency to increase isolates in Pseudomonas spp. - from 19 in 2017 to 30 in 2018, as well as in Serratia spp. Worrying is the isolation of Meropenem-resistant Kl. pneumoniae and S. aureus. The isolation of VRE (E. faecium) is also increasing. Data on isolated microorganisms by years are shown in Table 2.

Table 2: *Microbiological isolates by years*

Isolated microorganism	**2011**		**2016**		**2017**		**2018**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Acinetobacter spp.	46	19.6	61	14.5	45	14.5	35	13.5
E. coli	41	17.5	78	18.5	45	14.5	15	5.8
S. aureus	27	11.5	26	6.2	18	5.8	10	3.8
CoNS	28	12	66	15.7	35	11.3	29	11
Klebsiella spp.	28	12	55	13	42	13.5	36	13.6
Pseudomonas spp.	23	9.8	22	5.2	19	6.1	30	11.4
Serratia spp.	17	7.3	3	0.7	6	2	8	3
Enterococcus spp.	14	6	40	9.5	26	8.3	18	6.7
Enterobacter spp.	4	1.7	26	6.1	32	10.3	29	11.2
St. pyogenes	2	0.9	-	-	-	-	1	0.4
St. viridans	2	0.9	6	1.4	1	0.3	-	-
Proteus spp.	1	0.4	20	4.8	24	7.7	7	2.6
St. agalactiae	1	0.4	-	-	-	-	1	0.4
Xanthomonas maltophilia	-	-	3	0.7	2	0.6	4	1.5
S. pneumoniae	-	-	2	0.5	-	-	1	0.4
S. haemoliticus	-	-	-	-	-	-	1	0,4
S. epidermidis	-	-	-	-	-	-	3	1,1
S. cohnii	-	-	-	-	-	-	1	0,4
Corynebacterium spp.	-	-	2	0,5	-	-	-	-

Moraxella spp.	-	-	2	0,5	-	-	-	-
Citrobacter spp.	-	-	1	0,2	-	-	4	1,5
Clostridium ramosum	-	-	-	-	-	-	3	1,1
Rhizobium radiobacter	-	-	-	-	1	0,3	-	-
Sphingomonas paucimobilis	-	-	-	-	1	0.3	-	-
Achromobacter spp.	-	-	-	-	-	-	2	0.8
Bacillus megaterium	-	-	-	-	-	-	1	0,4
Rhodotorula spp.	-	-	-	-	-	-	1	0,4
Morganella morganii	-	-	-	-	-	-	3	1,1
Aeromonas salmonicida	-	-	-	-	-	-	1	0,4
Candida spp.	-	-	8	2	13	4.2	18	6.7
Bergeyella spp.	-	-	-	-	1	0,3	-	-
Trichosporon spp.	-	-	-	-	-	-	1	0,4
Total number:	**234**	**100%**	**421**	**100%**	**311**	**100%**	**263**	**100%**

It is evident that the number of isolates is the lowest in 2011 and twice as high in 2016, although the total number of surgical interventions in 2011 is almost the same as in 2016, 610 and 606 heart surgeries, respectively. In addition, DIS development rate was 1.7 times higher in 2016. Data for the 1st quarter of 2019 show the lowest number of isolated microorganisms - 39. VRE has not been isolated, but the problem with meropenem-resistant strains of Kl. Pneumonia persists (83.33%).

4.2. Superficial wound infections

Patients with superficial wound infections are diagnosed according to CDC criteria. Patient follow-up is retrospective and covers the period from October 2002 to June 2019. For this purpose, data from the medical documentation and the hospital archives were used. During this period, 637 (6.18%) of all operated patients (10307) with open heart surgery developed superficial wound infections.

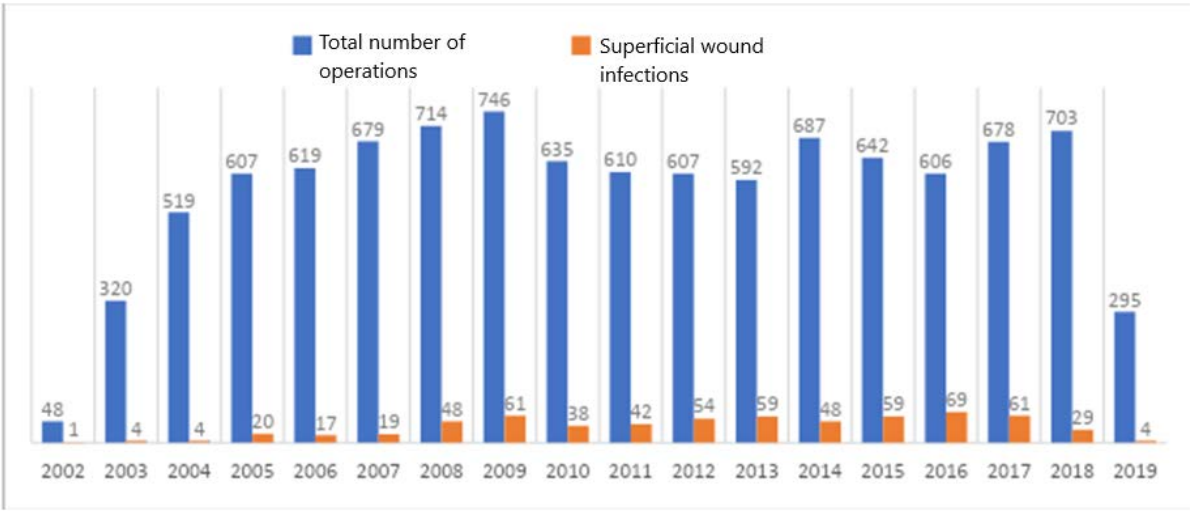


Diagram 2: *Distribution of superficial wound infections by years*

The diagnosis in 66% (420 operated) of them was made during the first follow-up examination after discharge from the clinic (10±3 days after surgery). 32% (204 operated) were diagnosed after 20 postoperative days. 2% (13 operated) developed a superficial wound infection before dehospitalization. The average age is 68.25 (41 to 88 years) and the male: female ratio is 2.02: 1.

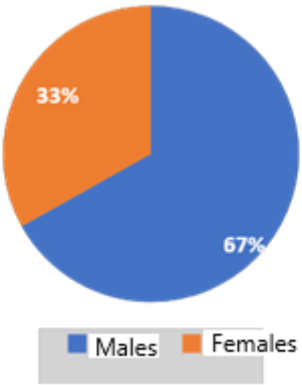


Diagram 3: *Distribution of superficial infections by sex*

Most often superficial wound infections develop in patients after coronary artery bypass grafting (ACP) - 34.2%, which is one of the main risk factors for the development of this type of disease.

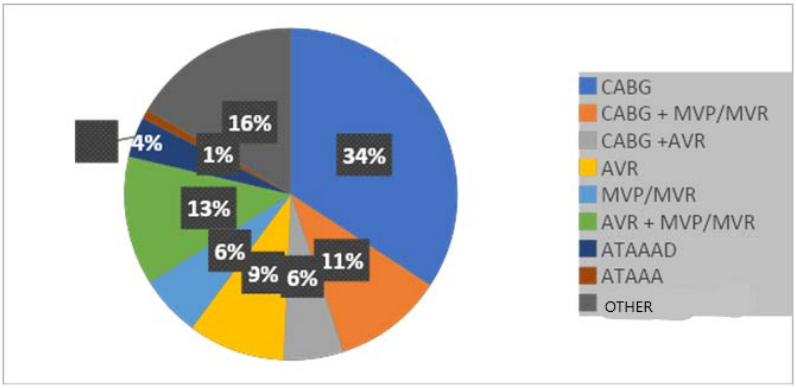


Diagram 4: *Distribution of superficial wound infections according to the type of operation*

Risk factors were identified and analyzed according to the STS model developed in 2005, which assesses the pre- and intraoperative risk of wound infections. A total of 13 factors were included: age, BMI, diabetes mellitus, renal failure, congestive heart failure, chronic limb arterial insufficiency, female gender, COPD, cardiogenic shock, myocardial infarction, surgery complexity, ECC time, intraaortic balloon (IABP). Some of the presented risk factors have been added or modified in the present dissertation. Anemia, thrombocytopenia, dual antiplatelet therapy preoperatively are included due to the fact that these conditions lead to an increased risk of re-exploration of the surgical wound due to bleeding.

Table 3: *Risk factors for the development of superficial surgical site infections*

Risk factors	**Superficial wound infections (n = 637)**	**%**
Emergency surgery	74	11.6
Obesity	92	14.4
Heart failure	65	10.2
Cerebrovascular disease	71	11.1
COPD	55	8.6
Diabetes mellitus	170	26.7
Peripheral artery disease	38	6
Status post radiotherapy/ chemotherapy	15	2.4
Renal failure	39	6.1
Chronic Dialysis (end-stage renal disease)	6	0.9
Status post mastectomy	7	1.1
Anemia	49	7.7
Thrombocytopenia	13	2
Dual antiplatelet therapy	87	13.7

Duration of ECC over 120 minutes	21	3.3
Cirrhosis	5	0.8
Ethylism	6	0.9
Smoking	130	20.4
Osteoarthritis	21	3.3

40.5% of patients have one risk factor, and 29.7% of them have more than 1 risk factor.

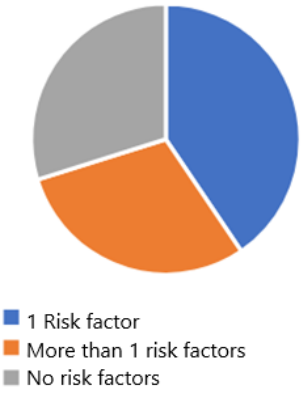


Diagram 5: *Number of risk factors*

In all 637 patients who developed superficial wound infections after open heart surgery, microbiological samples were taken from the wound for culture. The results of the microbiological studies are presented in Table 4. In 22 of the patients no microbiological agent was isolated. Gram (+) bacteria predominate. In 10 of the patients more than 1 microbial agent was isolated.

Table 4: *Isolated microorganisms in patients with superficial wound infections*

Isolated causative agent	**Superficial wound infections (n = 637)**	**%**
Staphylococcus aureus	148	23.4
CoNS	165	25.9
Enterococcus faecalis	52	8.2
Acinetobacter baumanii	45	7.1
Escherichia coli	66	10, 4
Klebsiella pneumoniae	58	9.1
Enterobacter cloacae	40	6.3
Pseudomonas aeruginosa	31	4.7
Staphylococcus aureus + E.coli	6	0.9
Staphylococcus aureus + Kl.pneumoniae	4	0.6
Sterile culture	22	3.4

Patient treatment includes AB, wound debridement and daily sterile dressings. AB treatment begins immediately after the wound infection is diagnosed. Empirical therapy with cefuroxime, vancomycin or dalacin C is initiated. Once a microbiological agent has been identified, AB treatment is in accordance with the data from the antibiogram. In 27.8% (177 patients) VAT was administered. In 419 (65.8%) of the patients a secondary suture of the operative wound was performed without prior application of VAT, and in the others the wound healed secondarily. The assessment of the method of treatment is made by the treating surgeon and the head of the clinic, taking into account the patient's condition, the size of the wound defect, the amount and type of wound secretion, the type of the isolated microorganism. In patients without VAT, dressings are changed daily by treatment with a solution of povidone-iodine (Braunol). Other dressings were also used (Bactigrass - linen tulle impregnated with white paraffin with 0.5% chlorhexidine acetate; Acticoat 3 and Acticoat 6 - nanocrystalline silver dressings; Intrasite Gel). When applying silver-impregnated dressings, the latter are changed every 72 hours.

In patients with VAT, dressings are changed every 72 hours and the pressure varies from -75mmHg to -125mmHg. For creating a negative pressure in the wound we use VISTA™ Negative pressure wound therapy system and RENASYS TM Negative pressure wound therapy system (Smith&Nephew Laboratory).

Secondary suturing is undertaken in wounds with a larger soft tissue defect with well-developed granulation tissue, lack of necrotic areas, minimal or no secretion and 2 sterile microbiological results from culture examination.

Surgical intervention for secondary suturing of the wound is performed under general or local anesthesia. The assessment is made after consultation with an anesthesiologist. The coagulation status is examined in advance and the anticoagulants (Sintrom, Rivaroxaban) and the antiplatelet agents (Clopidogrel, Ticagrelor, Prasugrel) are temporarily stopped if necessary. In patients with valve prosthesis, low molecular weight heparin is administered pre- and postoperatively until the target levels of INR (prothrombin time) are reached after Sintrom administration. In coronary patients after CABG or in those with an implanted intracoronary stent, antiplatelet therapy includes only Aspirin. In the operating room, the skin around the wound is cleaned with an alcoholic solution of povidone-iodine (Braunoderm), and the wound defect itself is cleaned with an aqueous solution of povidone-iodine (Braunol). In the presence of fibrin deposits or small areas of necrosis, the latter are excised, the wound edges are refreshed, thorough hemostasis is performed, the subcutaneous tissues are sutured with single absorbable sutures, and the skin is sutured with single polyamide sutures.

Results

The average hospital stay is 13 days. There are no reported cases of in-hospital mortality. Patients were followed up for 3 months. 1 dies 4 weeks after discharge from intracerebral hemorrhage. Two of them, treated without VAT, developed a deep wound infection of the sternum, which required rehospitalization and treatment of DIS. Wound edge necrosis is observed in 60 of the patients (9.42%).

4.3. Sternocutaneous fistulas

The study is retrospective and covers the period from October 2002 to June 2019. For the studied period 35 (out of 10307 operated) patients (0.34%) were admitted and treated in the Clinic of cardiac surgery at the University Hospital "St. Georgi" with a diagnosis of SCF. 8 of them are after treatment for DIS. The diagnosis is made in the presence of a fistula between the sternum (mediastinum) and the skin, secretion from it and positive microbiological results from a culture test. In some cases, fistulography and/or computed tomography are required to determine the exact location of the inflammatory focus. The sex ratio is 1.18: 1, and in men the incidence is slightly higher. The mean age of patients with SCF was 67.26 (45 to 87 years).

The time of onset of SCF is calculated depending on the time of the last surgical intervention to the sternum. According to this, the time of onset of SCF in the study group varies from 3 weeks to 5 years (average 1 year and 8 months). The frequency of SCF by years is presented in Figure 6.

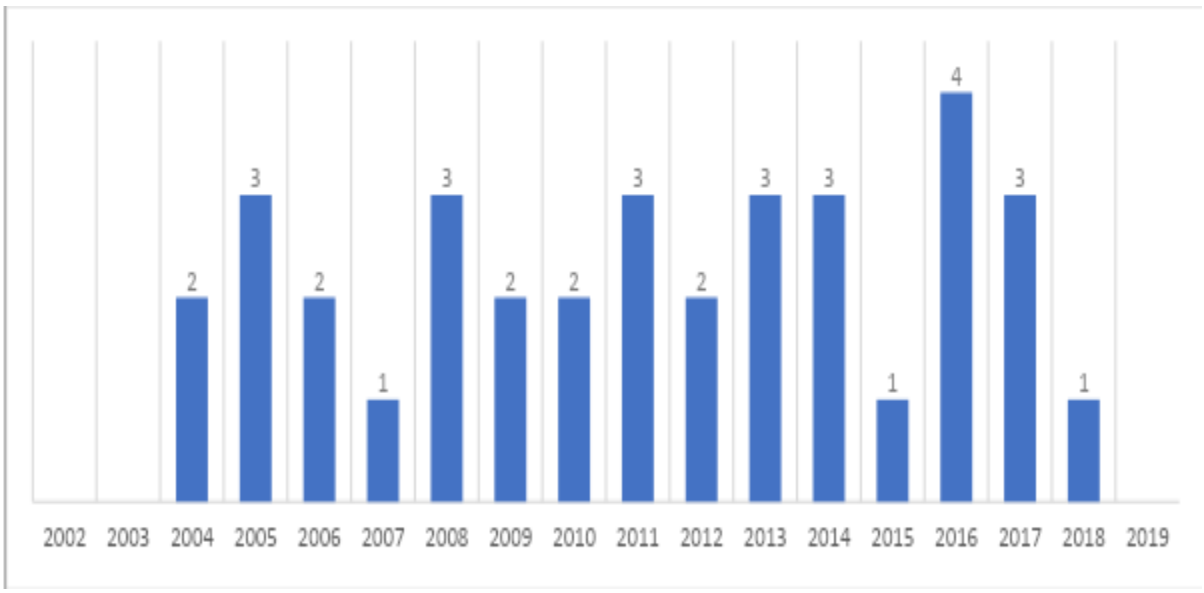


Diagram 6: *Frequency of SCF by years*

SCF most often develops in patients after CABG, as it is in superficial and deep wound infections.

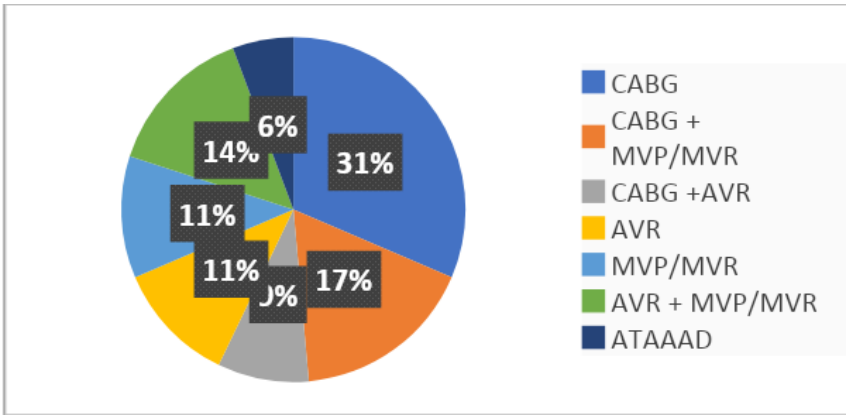


Diagram 7: *Distribution of SCF by type of cardiac surgery*

In the analysis of risk factors it became clear that obesity, diabetes and smoking are of the greatest importance, as in 19 (54.3%) patients there is 1 risk factor, and in 8 (22.9%) the risk factors are more than 1.

Table 5: *Risk factors*

Risk factors	**Sternocutaneous fistulas (n = 35)**	**%**
Emergency surgery	5	14.3
Obesity	12	34.3
Heart failure	6	17.1
Cerebrovascular disease	4	11.4
COPD	5	14, 3
Diabetes mellitus	8	22.8
Peripheral artery disease	3	8.6
Status post radiotherapy/ chemotherapy	2	5.7
Renal failure	3	8.6
Chronic Dialysis (terminal renal failure)	1	2.8
Status post mastectomy	1	2.8
Anemia	2	5 , 7
Dual antiplatelet therapy preoperatively	3	8.6
Duration of ECC over 120 minutes	2	5.7
Smoking	8	22.8
Osteoarthritis	1	2.8

In all 35 patients who developed SCF after open heart surgery, microbiological samples were taken from fistula for cultural examination (Table

6). No microbiological agent was isolated in 1 of the patients. Gram (+) bacteria predominate among the others, as in patients with superficial wound infections.

Table 6: *Isolated microorganisms in patients with SCF*

Isolated causative agent	**Sternocutaneous fistulas (n = 35)**	**%**
Staphylococcus aureus	12	34.3
CoNS	9	25.6
Enterococcus faecalis	4	11.4
Escherichia coli	2	5.7
Candida albicans	2	5.7
Pseudomonas aeruginosa	3	8.6
Proteus mirabilis	1	2.9
Klebsiella pneumoniae	1	2.9
Sterile culture	1	2.9

The treatment of SCF is complex and includes AB treatment according to the isolated microbiological agent and various surgical approaches. Empirical AB therapy with cefuroxime, vancomycin or dalacin C is initiated. Once the microbiological cause has been identified, AB therapy is guided according to the data from the antibiogram. The operation is performed under general or local anesthesia. An anesthesia consultation is performed. Coagulation status is examined and the same principles of anticoagulant and antiplatelet treatment are followed as described for superficial wound infections. In 14 of the patients, SCF was treated in one step. The fistula is excised to vital surrounding tissues and deep to the sternum. All foreign objects visible in the area of excision (osteosynthetic wires, pacing electrodes, sutures) are removed. The wound is sutured. In other patients in whom computed tomography reveals osteomyelitis in the sternum, which is confirmed intraoperatively, the fistula is excised, bone sequesters are removed. Then a VAT system is installed, which is changed every 72 hours. The duration of VAT is determined by the local status of the wound - secretion, the presence of granulation tissue, as well as microbiological results. As a rule, the wound is sutured secondarily after 2 sterile cultures obtained. As in superficial wound infections, the skin edges are refreshed, the subcutaneous tissue is sutured with single absorbable sutures, and the skin is sutured with single polyamide sutures.

Results

The average stay of patients in the clinic is 22 days. There are no reported cases of in-hospital mortality. Recurrence of the disease is registered in 12

patients (34.3%), 7 of whom were from the group treated with a one-step approach and 5 were from the group treated with VAT. They are rehospitalized and treated again. 4 of the patients required even more rehospitalizations, but 2 of them refused surgical treatment.

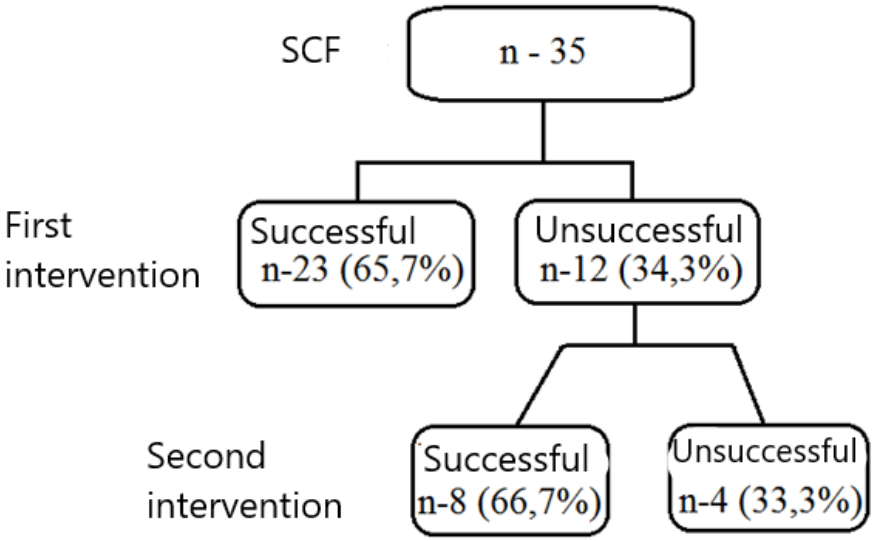


Figure 1: *Results*

4.4. Deep wound infections

The study is retrospective and covers the period from October 2002 to June 2019. For the studied period 146 (1.42% of 10307 operated) patients were treated in the Clinic of cardiac surgery at the University Hospital "St. Georgi ” with a diagnosis of deep sternal infection. The CDC criteria were used to define DIS.

When patients with DIS are hospitalized or when this diagnosis is suspected in patients who have not been discharged after cardiac surgery, fever, serum glucose levels, white blood cell count, CRP, and ultrasound evaluation of EF are assessed. Only 18 (12.4%) were afebrile, with a subfebrile temperature being 51 (34.9%). Body temperature > 38°C (52.7%) was reported in 77 of the patients (Table 7).

Table 7: *Clinical and laboratory parameters of the studied group of patients with deep wound infections (n=146)*

Indicators	**Mean ± SD**	**Median**	**Min**	**Max**	**95% CI**
Fever	37.73 ± 0.71	37.60	36.20	40.00	[37, 62; 37.85]
CRP	100.50 ± 40.33	98.00	15.00	326.00	[93.90; 107.09]
Leukocyte count	13.83 ± 4.44	13.10	4.40	29.50	[13.11; 14.56]
Serum glucose	8.35 ± 4.26	6.70	3.30	25.80	[7.66; 9.05]
EF	48.48 ± 10.54	50.00	17.00	74.00	[46.76; 50.21]

The risk assessment for cardiac surgery was performed, with the average EuroSCORE calculated at 8.35 (0.85 to 52.25).

All 146 patients hospitalized and treated for DIS in the clinic were classified according to the time of onset of infection after cardiac surgery - Pairolero and Arnold classification. Type I were 29 patients (19.86%), type II were 117 (80.14%). Type III includes SCF, which are considered separately.

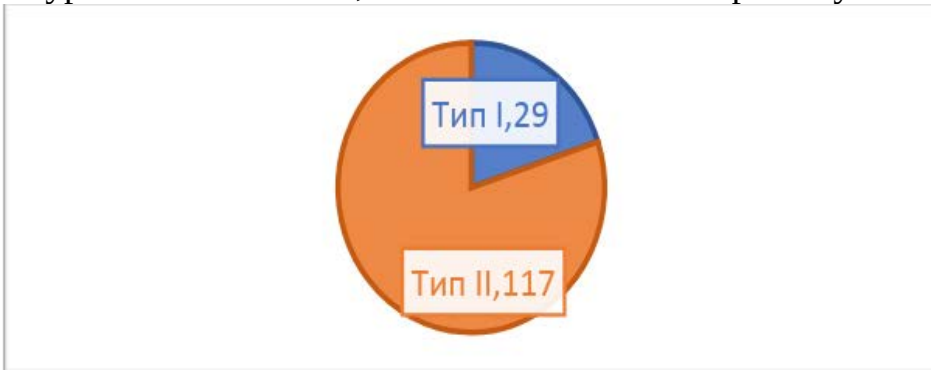


Diagram 8: *Distribution of patients with DIS according to the Pairolero and Arnold classification*

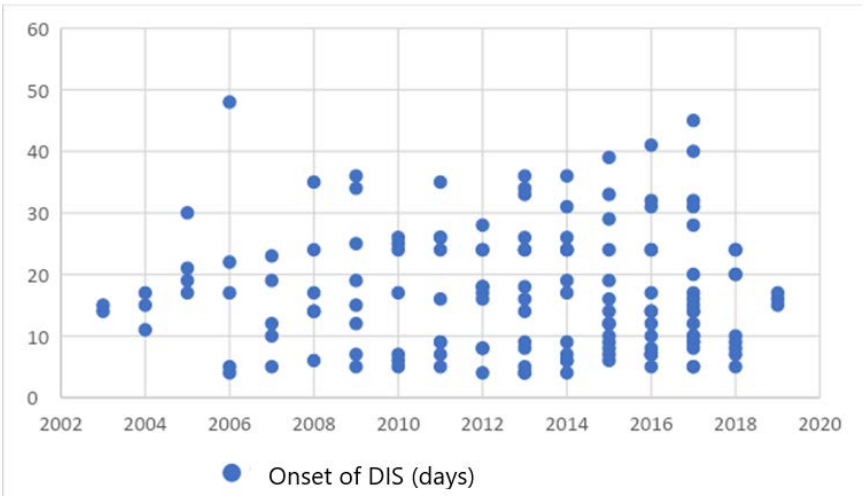


Diagram 9: *Time of onset of sternal infection after cardiac surgery by years*

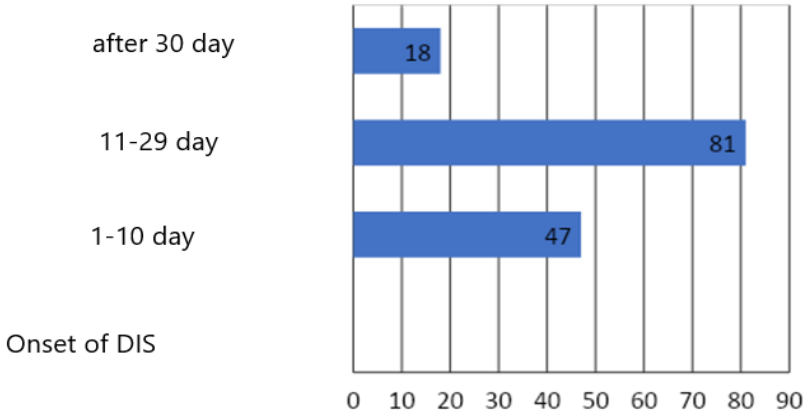


Diagram 10: *Time of onset of DIS postoperatively*

The charts show that patients are most often diagnosed with DIS and treatment begins about 2-3 weeks after heart surgery (average 17.2 days).

We observe a statistically significant upward trend for the studied seventeen-year period of the relative frequency in % of deep wound infections in relation to the number of open heart operations.

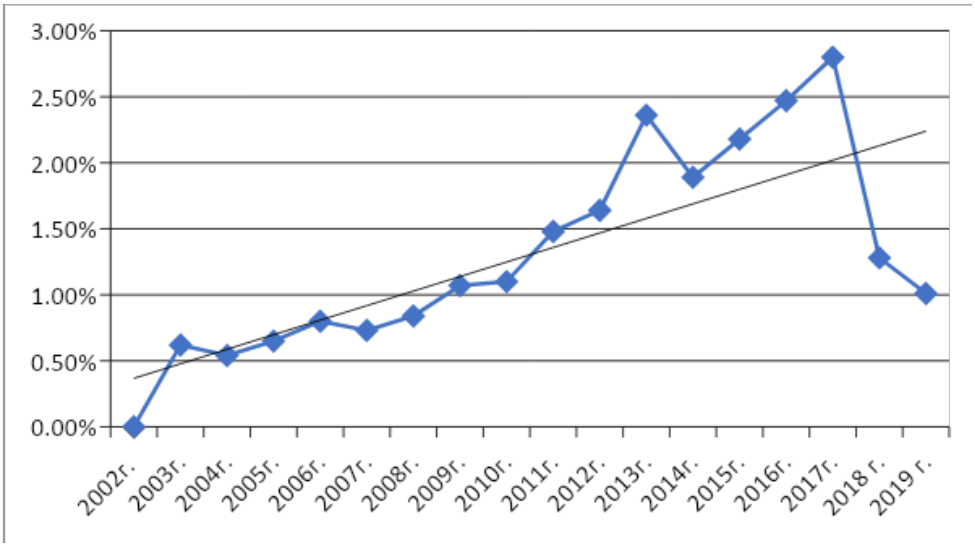


Diagram 11: *Dynamics of the frequency (in %) of deep wound infections in the period 2002-2019.*

The sex distribution is in favor of men. 98 of the patients were male and 48 were female. The male:female ratio was 2.04:1. The mean age of the patients was 65.4 years (29 to 85 years). When analyzing the age characteristics of the studied population, it became clear that the group of patients aged 61 to 70 years was at the highest risk of developing mediastinitis (Diagram 12). On the other hand, most heart surgeries were performed in this age group (Diagram 13).

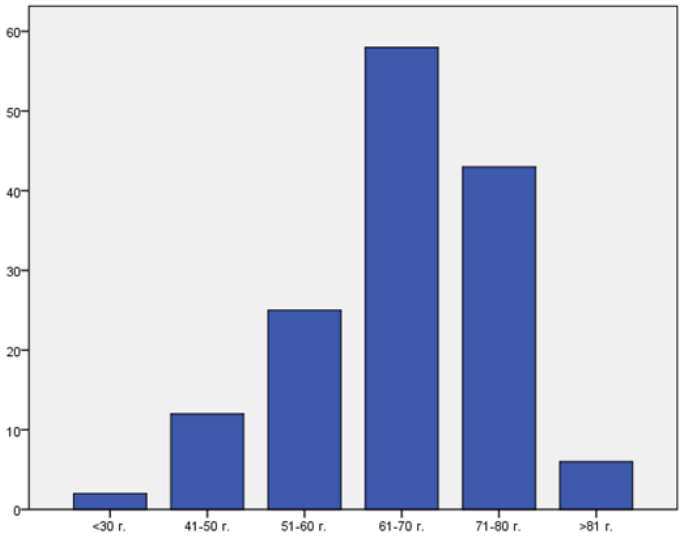


Diagram 12: *Distribution of patients with DIS by age groups*

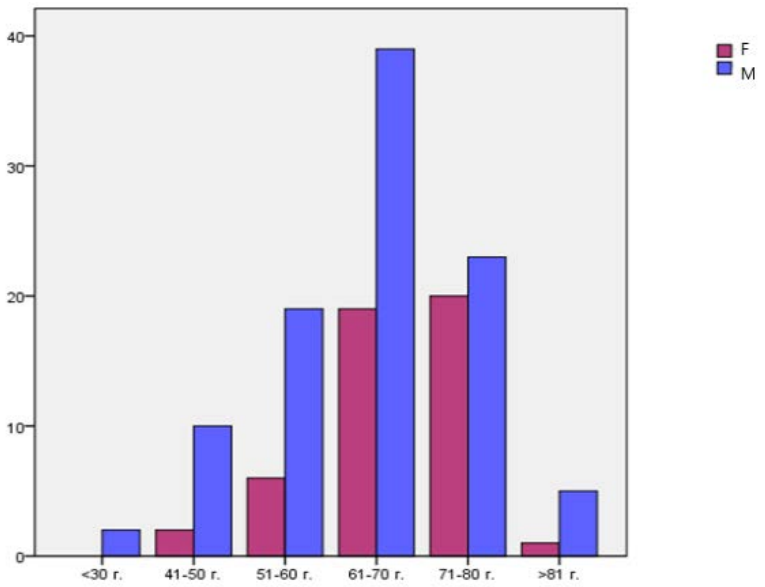


Diagram 13: *Relationship between age groups of patients and number of performed heart operations*

The analysis of risk factors revealed that only 18 (12.3%) of the patients were without known risk factors. 40 of them (27.4%) had one risk factor, and the remaining 88 (60.3%) had more than one risk factor. Among them, the most common are diabetes, heart failure, obesity and emergency surgery.

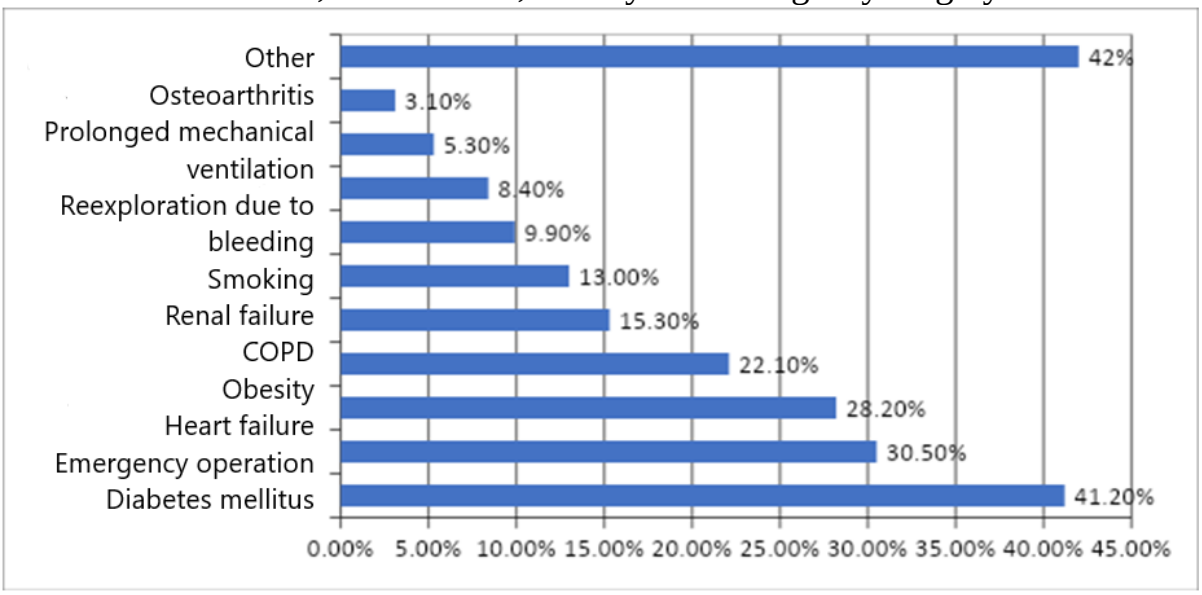


Diagram 14: *Frequency of the major risk factors in patients with deep wound infections*

to the "Other" are peripheral artery disease, cerebro-vascular disease, status post mastectomy, IABP, osteoporosis, Redo surgery, shock, cardiac massage, anemia, delirium, ethylism, chronic-ulcerative colitis, infectious endocarditis.

As in superficial wound infections and SCF, deep sternal infections most often develop in patients after CABG. There are 2 reoperations for prosthetic valve endocarditis.

Table 8: *Distribution of patients with DIS by type of cardiac surgery*

Intervention	**N**	**%**
CABG	65	44.5
CABG + MVP/MVR	16	10.9
CABG + Left ventricular repair	4	2.7
CABG + AVR + MVP/MVR	6	4.1
CABG + AVR	18	12.4
CABG + TVP	2	1.4
CABG + MVP/MVR + TVP	4	2.7
Bentall operation	2	1.4
OPCAB	1	0.7
AVR	10	6.8
MVP/MVR	8	5.5
ReAVR	2	1.4
TVR	1	0.7
Aortic resection for dissection	6	4.1
Myxoma extirpation	1	0.7

In all 146 patients who developed deep wound infections after open heart surgery, microbiological samples from the wound are examined (Table 9). In 18 (12.3%) of the patients no microbiological agent was isolated. More than 1 causative agent was isolated in 7 (4.8%) patients.

Table 9: *Isolated microorganisms in patients with DIS*

Isolated microorganism	**N**	**%**
CoNS	23	15.8
S. Aureus	21	14.4
E. coli	14	9.6
Kl. pneumoniae	12	8.2
A. baumanii	16	10.5
Ps. aeruginosa	9	6.3
S. marcescens	2	1.4
E. faecalis	7	4.8
P. mirabilis	9	6.3
P. vulgaris	2	1.4
E. cloacae	6	4.1
Cl. Pneumonia + A. baumanii	2	1,4
S. marcescens + Ps. aeruginosa	1	0.7

S. aureus + E. coli	2	1.4
E. coli + P. vulgaris	1	0.7
E. cloacae + A. baumanii	1	0.7
Sterile culture	18	12.3

Patients with DIS are divided into three groups, according to the type of surgical technique used in the treatment:

- Group I - wound debridement and refixation was performed with subsequent irrigation of the mediastinum with antiseptic solution;
- Group II - debridement of the wound was performed and VAT was applied, in the second stage the sternum was fixed;
- Group III - a method for reconstruction of the chest wall using soft tissue flap is applied.

Table 10: *Distribution of patients by groups according to the operative technique*

Group I - refixation with irrigation		**Group I - BAT with refixation**		**Group III - Soft tissue flap**	
N	**%**	**N**	**%**	**N**	**%**
61	41,8	68	46, 6	17	11.6

The decision on which of the operative techniques to apply was made by the treating surgeon and the head of the clinic, taking into account the patient's condition, the time of infection, the isolated microorganism and the surgical experience of the team. In Group III patients, a flap of omentum majus was used for chest wall reconstruction, except in 1, in which a flap of m. rectus abdominis was interposed. In 1 of the patients, in addition to omentoplasty, a titanium plate was implanted. Empirical AB treatment is initiated in all patients and then changed as needed according to the antibiogram data. In three of the patients who had a clinical presentation of severe sepsis, an innovative approach in cardiac surgery to remove the mediators of inflammation (cytokines, endotoxins) - oXiris filter (Baxter) was applied.

Results

The average stay of patients in the intensive care unit is 5 days (from 0 to 46 days), and the average total hospital stay is 15.6 days (from 5 to 55 days).

Table 11: *Hospital stay and ICU stay of the studied group of patients with deep wound infections (n = 146)*

Stay (days)	Mean ± SE	Median	Min	Max	95% CI
ICU	4.98 ± 0.74	3.00	0	46.00	[3, 51; 6.45]
Hospital	15.62 ± 0.71	13.00	5.00	55.00	[14.21; 17.02]

Table 12: *ICU stay and total hospital stay*

		N	Average stay (days)	SD	Std. Error	F	P
ICU stay	Group I	61	7.18	9,014	1,154	3,367	0.037
	Group II	68	3.65	9,698	1,176		
	Group III	17	2.41	1,583	0.384		
	Total	146	4.98	9	0.745		
Total hospital stay	Group I	61	15.43	8,287	1,061	1,426	0,244
	Group II	68	16.53	9.608	1.165		
	Group III	17	12.65	3.22	0.781		
	Total	146	15.62	8.582	0.71		

No statistically significant difference between the three groups in terms of total hospital stay (F = 1.426, P = 0.244), in contrast to the stay in intensive care unit where we found a statistically significant higher stay for patients in group I (F = 3.367, P = 0.037) (Table 12).

Complications that occurred in the postoperative period are summarized in Diagram 15.

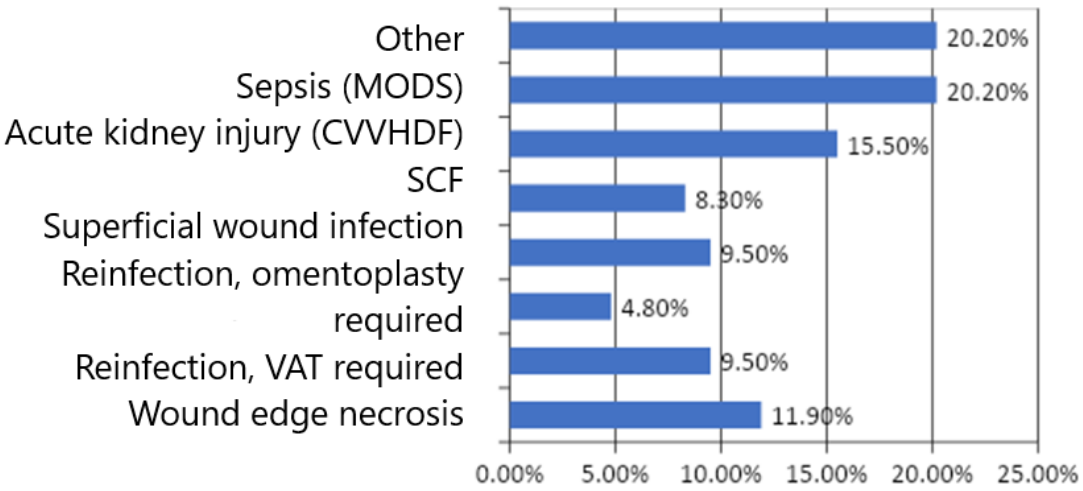


Diagram 15: *Frequency of major complications in patients with deep wound infections*

Divided into groups, complications are shown in Table 13.

Table 13: *Complications in patients with DIS*

	Method of treatment					
Complication	**Group I**		**Group II**		**Group III**	
	N	**%**	**N**	**%**	**N**	**%**
Cicatricial necrosis	2	1,4	4	2,7	4	2,7
Reinfection requiring VAT and refixation	5	3,4	3	2,1	-	-
Reinfection requiring omentoplasty	-	-	4	2,7	-	-
Superficial wound infection	5	3,4	2	1,4	1	0,7
SCF	3	2,1	4	2,7	-	-
AKI requiring CVVHDF	8	5, 5	5	3,4	-	-
Septic shock (MODS)	10	6,8	7	4,8	-	-
Other	6	4,1	10	6,8	1	0,7

The column 'Other' includes mesenteric thrombosis - in 1 of the patients, transient ischemic attacks - 1, pulmonary embolism - 2, stroke - 2, cardiogenic shock - 1, hemorrhage due to heart injury - 2, postoperative hernia - 1, urinary tract infection - 1, pneumonia - 3, reoperation - 1, gastro-intestinal hemorrhage - 1, empyema - 1. The table shows that there is therapy failure in 5 patients from

Group I, which requires re-intervention - VAT and refixation. In Group II, re-intervention was required in 7 of the patients. In 3 - VAT and refixation, in 4 - omentoplasty (in 2 and titanium plate implantation). The most common complications are AKI, requiring hemofiltration and septic shock, and they are the main cause of death. No cases of reinfection were reported in Group III. In 1 patient in this group, anterior abdominal wall plastic surgery was performed using a polypropylene mesh (Ethicon) 4 months after surgery due to an epigastric postoperative hernia.

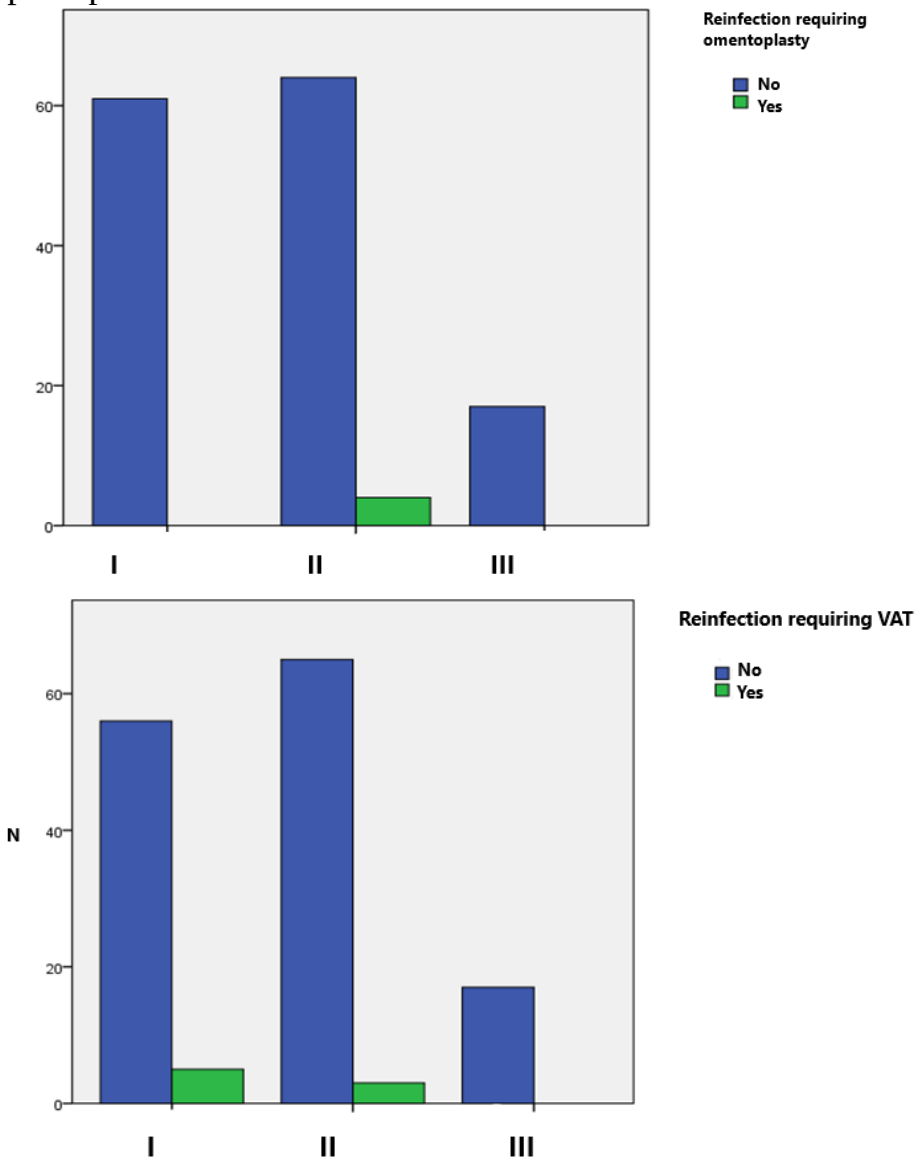


Diagram 16: *Failure of the operative technique in the three groups of patients*

Rehospitalization within 1 year is required in 21 patients (14.4%), and in 2 of them it is not associated with complications of the operative wound. There is no intraoperative mortality. Perioperative mortality occurred in 1 of patients in group I, who developed disseminated intravascular coagulation syndrome and died 12 hours after refixation from hemorrhagic shock. Early postoperative

mortality was 8.9% (13 patients). 1 patient died of stroke, 2 - of pulmonary thromboembolism, 1 - of heart failure (cardiogenic shock), 1 - of hemorrhagic shock (due to rupture of the right ventricle from the edge of the sternum - Group II). The others had a clinical manifestation of severe sepsis and MODS. After the 30th day of the operation, 6 of the patients (4.2%) died. The cause of death in 1 of them is severe gastrointestinal hemorrhage (hemorrhagic shock), in 1 - mesenteric thrombosis, 1 - rupture of a graft to the right coronary artery (Group II), in 3 - severe sepsis with MODS. The overall postoperative mortality in patients with sternal infections was 13.7%.

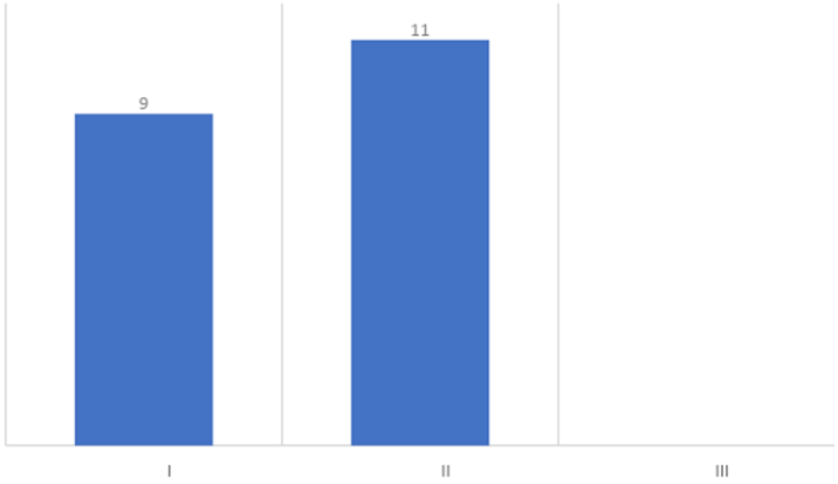


Diagram 17: *Postoperative mortality in patients with DIS, compared by groups*

In the statistical processing of the data, it is clear that there is no significant difference in complications and postoperative mortality in patients from the three groups, although in Group III no mortality was reported and complications were significantly less. This is explained by the small number of patients operated on by this method.

4.5. Results - study of predictive biomarkers for wound infections and septic conditions

For the period July 2017 - February 2018, we prospectively examined 137 elective coronary patients in order to analyze the prognostic value of a panel of laboratory biomarkers proposed by our institution. Patients with clinical and laboratory evidence of infection - fever, leukocytosis, toxicoinfectious syndrome and elevated CRP were excluded from the study. Troponin, CC, CC-MB, Pro-BNP and hs-CRP were measured prior to surgical intervention. Troponin, CC, CC-MB, ALT, AST, lactate, CRP and PCT were measured 24 hours after the open heart surgery. Patients were followed within 3 months and postoperative results were assessed.

In statistical analysis of data, PCT is a major predictive marker for the development of SIRS, sepsis, superficial and deep wound infections. It is more specific and more sensitive than CRP. PCT values above 2 ng/ml are associated with an extremely high risk of developing wound infections.

Table 14: *Analysis of the predictive value of procalcitonin with respect to the studied complications*

Complications	**AUC**	**SE**	**95% CI**	**P value**
Superficial wound infections	0.872	0.045	[0.783; 0.961]	0.001
Deep wound infections	0.906	0.032	[0.844; 0.968]	0.001
SIRS	0.893	0.032	[0.830; 0.956]	0.0001
Sepsis	0.847	0.041	[0.767; 0.927]	0.001

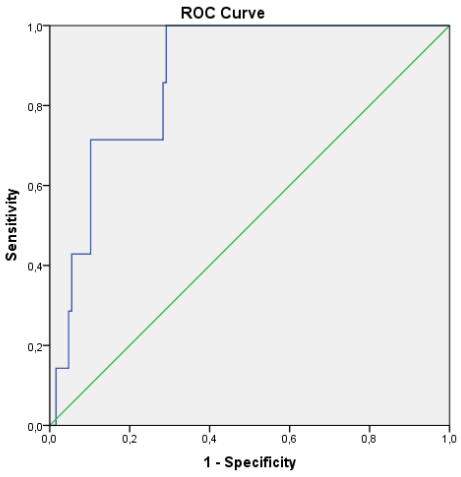


Diagram 18: *ROC curve of sensitivity and specificity of procalcitonin to superficial wound infections*

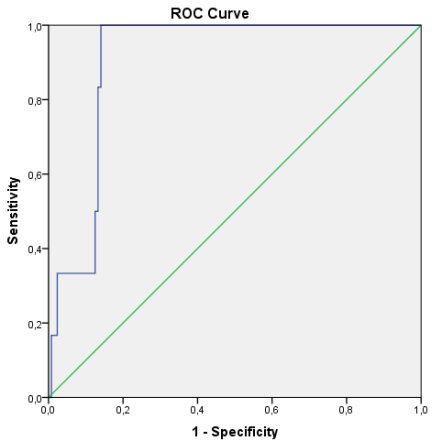


Diagram 19: *ROC curve of sensitivity and specificity of procalcitonin to deep wound infections*

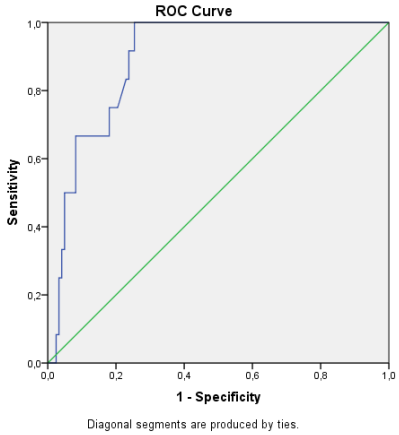


Diagram 20: *ROC curve of sensitivity and specificity of procalcitonin of SIRS*

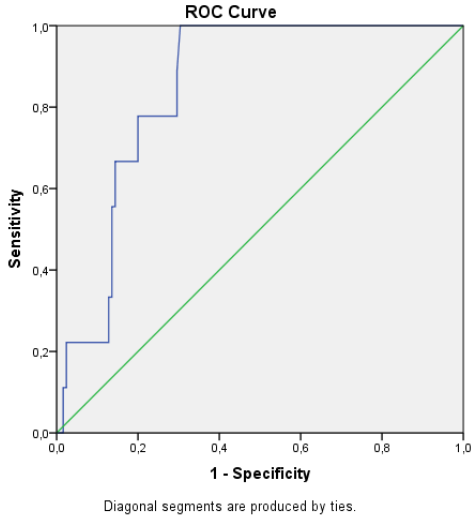


Diagram 21: *ROC curve of sensitivity and specificity of procalcitonin with respect to sepsis/septic shock*

The other biomarkers turned out to be statistically insignificant as predictors of wound infections, but in their analysis interesting conclusions can be drawn, which are presented in the discussion.

4.6. Results - application of preventive measures for wound infections

The increase in the occurrence of wound infections in the recent years has necessitated the search for alternative techniques for the prevention of these potentially fatal complications. The study is prospective and covers the period from January 1, 2018 to January 1, 2019. Patients were divided into 2 groups. In Group I (n = 300) an innovative protocol for pre-, intra- and postoperative prophylaxis was applied, and in Group 2 (n = 300) the standard for the clinic methods were applied. Preoperative prophylaxis in Group I included screening for nasal carriers of S. aureus and its eradication (in case of isolation) with nasal ointment mupirocin 20 mg/g. Patient preparation and AB prophylaxis have also been modified. Before the metal osteosynthesis of the sternum, a vancomycin paste is placed on the sternal edges, and the subcutaneous tissue is irrigated with a gentamicin solution, having previously been tested for allergy to the indicated AB. In patients with BMI>30 kg/m^2 Robicsek technique is used. A protocol for early rehabilitation and gradual increase of physical activity was applied postoperatively, unlike the standard restrictive regimen in the clinic.

The mean age of the patients in the two groups was 66.06 (32 to 87 years) and 66.36 (19 to 86 years), respectively. The sex ratio is presented in Diagram 22.

Diagram 22: *Gender distribution of patients in both groups*

It is evident that men predominate in the population of both groups, which is explained by the fact that men suffer from atherosclerotic heart disease 2 times more often from women.

Table 15: *Risk factors in the studied groups*

Indicator	**Group 1 (n = 300)**		**Group 2 (n = 300)**		***p***
1 risk factor	122	40.7%	140	46.7%	0.14
More than 1 risk factors	103	34.3%	71	23.7%	**0.004**

Table 16: *Comparison of risk factors by groups*

Risk factors	Group I (n = 300)		Group II (n = 300)		*p*
Emergency operation	50	16.7%	50	16.7%	1
Obesity	37	12.3 %	33	11%	0.61
Heart failure	38	12.7%	31	10.3%	0.37
Cerebrovascular disease	36	12%	38	12.7%	0.8
COPD	25	8.3%	22	7.3%	0, 65
Diabetes mellitus	82	27.3%	66	22%	0.13
Peripheral artery disease	15	5%	9	3%	0.21
Status post radiation therapy/ chemotherapy	10	3.3%	8	2.7%	0.63
Renal failure	15	5%	16	5.3%	0.86
Chronic Dialysis (end-stage renal disease)	2	0.7%	2	0.7%	1
Status post mastectomy	4	1.3%	2	0.7%	0.41
Anemia	29	9.7%	22	7, 3%	0.31
Thrombocytopenia	5	1.7%	6	2%	0.76
Dual antiplatelet therapy preoperatively	35	11.7%	30	10%	0.51
Duration of ECC over 120 minutes	13	4.3%	12	4%	0.84
Cirrhosis	3	1%	3	1%	1
Ethylism	5	1.7%	4	1.3%	0.73
Smoking	56	18.7%	50	16.7%	0.52
Osteoarthritis	8	2.7%	10	3.3%	0.63

The incidence of diabetes mellitus in Group I patients is slightly higher.

Results

Patients from both groups were followed up within 3 months after discharge and postoperative results were reported and analyzed. 8 (2.7%) of Group I patients developed superficial wound infections and only 1 (0.3%) patient developed a deep sternal infection. In Group II, superficial and deep wound infections occur in 21 (7%) and 8 (2.66%) operated, respectively.

Table 17: *Presents the difference in the incidence of wound infections in the two groups*

	Group 1 (n = 300)	**Group 2 (n = 300)**
Superficial wound infections	8	21
Deep sternal infections	1	8

In contrast to 2017, when the peak of wound infections was registered - 8.99% superficial infections and 2.80% DIS, in 2018 they decreased twice - 4.12% for superficial wound infections and 1.28% for DIS.

Table 18: *Comparative analysis of wound infections for 2017 and 2018*

Year	**2017**	**2018**	***p***
Total number of operated patients	687	703	
Superficial wound infections	61	29	**0.0003**
Deep wound infections	19	9	**0.0488**

5. Discussion

Mediastinitis is a life-threatening condition that is associated with extremely high mortality if recognized late or treated incorrectly. Although long recognized as a complication of some infectious diseases, most cases of mediastinitis are associated with cardiac surgery (> 500,000 cardiac surgeries per year in the United States and over 5,000 in Bulgaria). The incidence of this complication is approximately 1-4%, depending on factors such as patient populations and study methodology. Although small in proportion, the actual number of patients affected by mediastinitis is significant. The incidence of DIS in the current study is 1.4%, which correlates with the results of reports by other authors on the topic. The reported incidence of superficial wound infections and SCF was 6.18% and 0.34%, respectively.

Table 19: *Incidence and mortality from mediastinitis in other large studies*

Author	Number of patients	Incidence of mediastinitis%	Mortality%
Loop	6504	1.1	14
Wouters	1368	1.7	30
Farinas	3645	0.9	35
Milano	6459	1.3	12
Valla	9814	1.0	39
Musoz	3711	2.2	18
Stéhle	13285	1.5	4
Bitcover	1935	2.1	12
Gerdlund	9557	1.3	19
Abboud	9136	0.5	23
Fowler	331429	0.9	17
Stoev et al.	10307	1.4	13.7

This dissertation demonstrates several important advantages. First, an in-depth analysis of the microbiological agents in the clinic was performed, which determines the adequate AB therapy. Secondly, all methods for diagnosis and treatment of superficial and deep wound infections and SCF, which occurred after open heart surgery, are presented and described in detail. Third, potential biomarkers and risk factors for these complications have been studied and analyzed. Fourth, effective and easily feasible methods for preoperative, intraoperative and postoperative prophylaxis have been introduced.

The most common microorganisms responsible for poststernotomy infections are CoNS and S. aureus. Other pathogens associated with these complications are Propionibacterium, Acinetobacter, Enterobacter cloacae, Escherichia coli and Klebsiella. There is a subset of patients with sternotomy wounds in whom no pathogen has been isolated and who are considered to have

non-infectious sternal dehiscence. Olbrecht et al. examined 12,380 patients after median sternotomy from 1994 to 2004 and found 48 (0.39%) patients with this condition. Most of them had complaints of pain or instability of the sternum, while others had serosanguine secretion from the wound. In some cases, the course was completely asymptomatic. According to Gårdlund et al. postoperative mediastinitis can be divided into 3 types depending on the etiology and type of microorganism:

1. Mediastinitis associated with COPD, obesity and dehiscence of the surgical wound, usually caused by CoNS infection;
2. Mediastinitis resulting from perioperative contamination of the mediastinal area, often caused by S. Aureus infection;
3. Mediastinitis caused by the spread of concomitant infections (e.g. pneumonia or bacteremia), often associated with gram-negative bacteria.

Studies show that DIS caused by gram-negative microorganisms were often polymicrobial. The initiation of inappropriate antibiotic regimens leads to a higher incidence of secondary infections, prolonged mechanical ventilation and infusion of vasopressor agents, and increased 30-day mortality. Kotnis-Gąska et al. in 2018 monitored 164 patients with wound infections after open heart surgery and analyzed the microorganisms isolated from wound secretions. This study documented that Staphylococcus epidermidis, Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae and Pseudomonas aeruginosa are the most common causes of surgical site complications. Chaudhuri et al. prove in a study conducted between 2005 and 2011 that Staphylococcus aureus is the most common microorganism cultured in cases of mediastinitis (39%). Half of them are sensitive to methicillin. This is followed by CoNS (27%), and Gram-negative microorganisms were cultured in less than a quarter of patients (23%). Ps. aeruginosa is the most common Gram-negative bacterium isolated from wound secretions (6%). The pathogenic spectrum of poststernotomy infections may differ in different hospitals. In our institution, CoNS are the main cause of infection - about 25% during the study period. Moinipoor et al. in their study reported 82 (1.7%) cases of DIS, with mortality in patients with and without an isolated causative agent of 10.9% and 6.7%, respectively. The causative agents are Klebsiella, Pseudomonas, CoNS, Acinetobacter, Staphylococcus aureus, Escherichia coli and MRSA. Klebsiella is the most commonly isolated pathogen, which can be easily explained by the lack of routine AB prophylaxis for Gram-negative microorganisms in high-risk patients in their study. In our institution, the main perioperative antibiotic used for prophylaxis is cefuroxime, although AB regimens change according to the annual data for isolates. Our study shows that Klebsiella pneumoniae is the causative agent in about 8% of cases of mediastinitis. Polyresistant microorganisms are therapeutically problematic. 10 of the isolated S. aureus were MRSA, 8 of E. coli ESBL (+), at Kl. Pneumoniae 4 of the isolates are meropenem-resistant. There are 2 isolated VREs and 1 isolate of A. baumanii

resistant to colistin. Knowledge of the microbiological flora in the clinic or hospital generally helps in the correct selection of AB prophylaxis. Adequately initiated empirical antimicrobial therapy is one of the key points in the fight against infections. Due to the increase in the incidence of superficial and deep wound infections, we performed a retrospective analysis of the isolated microbiological flora in the clinic and AB resistance and compared the results for 2011, 2016, 2017 and 2018, for which the development of DIS is 1.48%, 2.47%, 2.80% and 1.28%, superficial wound infections 6.88%, 11.38%, 8.99% and 4.12% respectively. The analysis of the results shows that the number of isolates is the lowest in 2011 and twice as high in 2016, although the total number of surgical interventions in 2011 is almost the same as in 2016, respectively 610 and 606 cardiac operations. In addition, the DIS development rate was 1.7 times higher in 2016. This can be explained by the fact that the complexity of the operations increases, patients are polymorbid, the postoperative period is prolonged. In 2018, the number of isolated microorganisms is the lowest, which correlates with the newly established measures in the clinic for decolonization, innovative surgical and anesthesia techniques, adequate AB therapy and prevention, staff training and education. The data for the 1st quarter of 2019 show the lowest number of isolated microorganisms - 39. From the data for microbiological isolates by years it is evident that most often in percentage terms are isolated Acinetobacter spp., Klebsiella spp., E. coli , S. aureus, CoNS. Representatives of the genus Enterobacteriaceae are most often isolated from tracheal samples and/or blood cultures in patients with sepsis based on lung infection and less frequently from wounds. These patients usually have severe respiratory failure with inability to wean from mechanical ventilation. Acinetobacter is the cause of about 35-40% of ventilator-associated pneumonia. A large percentage of these patients have tracheostomy cannulas. Wound infections occur through contamination of mediastinal structures due to anatomical proximity. Data on isolated wound secretion bacteria demonstrate a predominance of CoNS and St. aureus as the main causes of wound complications. In patients with superficial wound infections CoNS and St. aureus were isolated in 25.9% and 23.4% of cases, respectively. In those with SCF CoNS and St. aureus were isolated at 25.6% and 34.3%, respectively. In cases of mediastinitis CoNS was isolated in 15.8%, St. aureus - 14.4%, A. baumanii - 10.5%, E.coli - 9.6%, Cl. Pneumoniae - 8.2%. Interestingly, in patients with DIS CoNS and St. aureus are also the main causes, but a large percentage of infections are due to members of the genus Enterobacteriaceae. In these cases, the mediastinal structures are secondarily infected - with concomitant infection of other organs and systems. Most often these patients require long ICU stay because of septic conditions.

Patients with DIS usually develop symptoms within 30 days after cardiac surgery. In addition to fever, other common signs include leukocytosis, elevated CRP, surgical wound dehiscence, purulent secretion, and sternal instability.

SCF can develop in chronic cases. In the present study, about 50% of patients with mediastinitis were diagnosed between 11 and 29 postoperative days (Pairolero and Arnold type II classification). Body temperature >38°C (52.7%) was reported in 77 of the patients, and CRP was above 100 mg/L in more than 70% of patients. Imaging techniques are helpful in establishing the diagnosis. Echocardiography allows assessment of the function of the left ventricle and the valvular apparatus of the heart, the condition of the pericardium, the presence of pericardial and/or pleural effusions. The method is easy to perform (even next to the patient's bed) and is non-invasive. However, echocardiography is not informative enough to diagnose DIS. Chest X-rays and contrast-enhanced CT scans are much more informative methods. X-rays may show enlargement of the mediastinum, pneumomediastinum, presence of pleural effusions. In case of total dehiscence of the sternum, displacement of the placed osteosynthetic wires is indicative, which is known in the literature as the "dancing wires" phenomenon. For preoperative assessment of patients and clarification of the extent of involvement of the mediastinum and soft tissues, computed tomography is mandatory in our institution. The method assesses the pre- and retrosternal space, the presence of gas and liquid collections in the mediastinum, dehiscence of the sternum and the integrity of the wires, the presence of bone sequesters and fistulas. Pleural effusions, encapsulations (if any) and soft tissues of the chest wall are also evaluated. In addition, the method may depict bone erosion, periosteal reaction, areas of sclerosis, and soft tissue edema. CT can show the exact spread of inflammation, which is crucial for planning the surgical treatment.

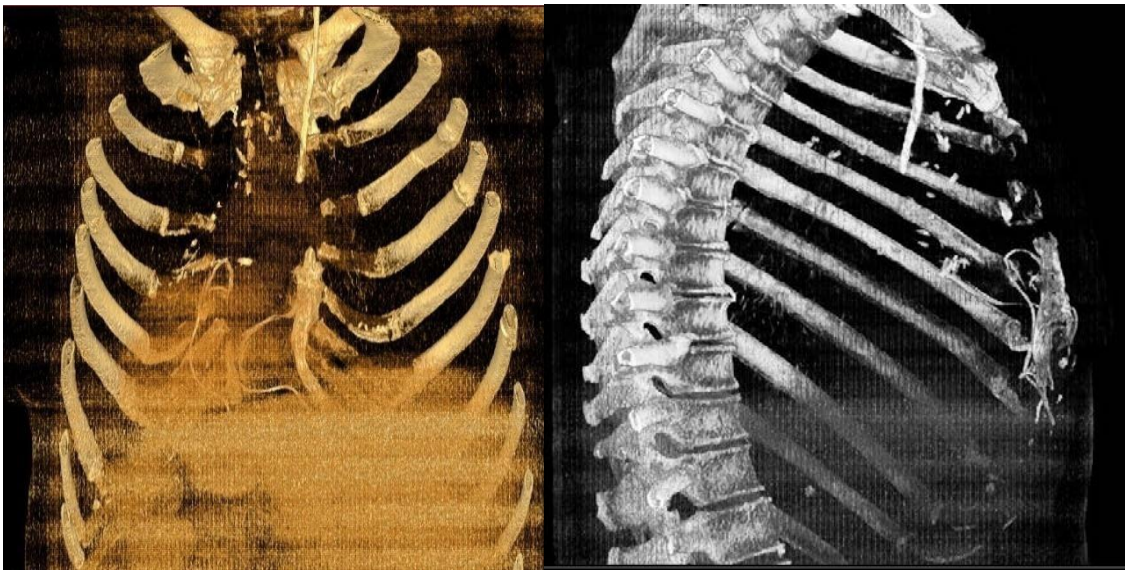


Figure 2: *Total destruction of the sternum in a 59-year-old woman after CABG. In this case, a titanium plate is implanted to stabilize the chest wall in combination with omentoplasty.*

The pathogenesis of wound infections is complex and multifactorial. Risk factors can be broadly divided into preoperative, intraoperative and

postoperative. Numerous studies have been conducted to identify risk factors, but to date no consensus has been reached on their individual contribution. Part of the problem arises from the different definitions of poststernotomy infections used in the different studies and the different characteristics of the study population. However, knowing the most common risk factors, it is possible to identify high-risk patients, apply preventive measures and initiate timely and adequate treatment. A number of scales and systems have been developed to assess and calculate the risk of developing wound complications after open cardiac surgery. However, there are no specific models for predicting DIS. The Gatti Scale is the first system to assess and predict the risk after using both internal thoracic arteries (BITA) and has been shown to be superior to existing point systems for posternotomy infections after CABG. A French cohort study found that this scale was effective, although more multicenter validation studies are needed before it could be incorporated into clinical practice. The latest model for risk stratification and forecasting of DIS after the CABG from Brazil is still awaiting external validation. Risk factors were identified and analyzed using the STS model developed in 2005, which assesses pre- and intraoperative risk of wound infections. The results of studies in the literature regarding risk factors for wound infections after open heart surgery studies are confusing. The data are mainly from the 1980s and 1990s (Table 20).

Table 20: *Risk factors for posternotomy infections in selected large studies*

Автор	N	Честота на раневи инфекции %	Възраст	Пол	Обезитет	Тютюнопушене	ЗД	ХОББ	ФИ	Предоперативен престой	Спешна операция	Времетраене на операцията	ВГА	Хиперхликемия	Хемотрансфузии	Продължителна механична вентилация	Реоперация	Престой в реанимация
Ottino	2579	1.9	-	-			-	+	-	+	-	-	+				+	-
Hammermeister	10634	1.6	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Loop	6504	1.1	-	-	+	-	+	-	-	+	-	+	-	-	+	-	-	-
Wouters	1368	1.7				+	-						-			+	+	
Blanchard	4137	0.1									+						+	
Farinas	3645	0.9									+	+				+	+	+
Milano	6459	1.3			+		+					+	+	-			+	
The Parisian	1830	2.3	-	-	+		-			-	-	-	+			-	+	
Valla	9814	1.0		+	+		+				+	+	+			+		
Antunes	2512	2.3	-	-	+	-	+		-		-		-			+	-	
Upton	5176	1.2					+		+	+								
Стоев и кол.	10307	4.4	-		+	+	+	+	+		+					+	+	

Only a few of the studies are newer and follow-up of patients is long-term - up to 15 years. Several shorter studies with fewer patients have been published, as well as several multicenter studies. Some focus only on mediastinitis, while

others consider superficial wound infections and SCF. In most of the reports, the data are entered prospectively in registers, but the collection of data on infectious complications is retrospective. Very few fully prospective studies are available. They are often focused on different risk factors, depending on the information entered in the registers. One of the main risk factors in most of the studies reviewed is obesity. Obesity is an independent risk factor that significantly increases the chances of developing wound infections by up to 2.6 times. Several hypotheses have been proposed to explain this relationship. The larger circumference of the chest wall puts more tension in the area of the operative wound, which results in instability and thus predisposes to dehiscence and infection. The reduced blood supply to adipose tissue leads to a delay in the healing process, and also the penetration of AB is less effective. In addition, physiological changes in obese individuals disrupt the pharmacokinetics and pharmacodynamics of drugs, making dosing a real challenge. Technical difficulties and long operating times contribute even more to the risk. In the present dissertation, obesity is one of the main risk factors for the development of complications of the operative wound. In patients who developed superficial wound infections, 14.4% of them had a $BMI \geq 30\ kg/m^2$. For SCF and DIS the percentages are 34.3% and 22.1% respectively. In a French study, 5.6% of patients were obese, which did not correlate with the data in our study. Diabetes mellitus is another risk factor strongly associated with the development of DIS. There is evidence that hyperglycemia has extremely detrimental effects on the immune system, which in turn impairs wound healing and increases the risk of infection. Hyperglycemia is associated with increased mortality, DIS and length of hospital stay. Perioperative glycemic control is essential to reduce the risk of developing wound infections. Trick et al. demonstrated that the risk of developing infections in patients with preoperative glucose concentrations above 11.1 mmol/L was 10 times higher than in well-controlled patients. In addition, Furnary et al. in a prospective study demonstrated that strict glycemic control (defined as blood glucose concentration <8.3 mmol/L) by prolonged intravenous insulin infusion during the perioperative period reduced the risk of DIS by up to 63%. In our institution, patients with hyperglycemia/diabetes are managed according to the same strategy. More than 70% of patients diagnosed with DIS had a serum glucose concentration above 10 mmol/L. Diabetes as a risk factor in the studied population is found in 26.7% - superficial wound infections, 22.8% - SCF, 41.20% - DIS. In a Finnish study of 557 patients with superficial and deep wound infections, the authors reported that 21% had diabetes.

The role that sex plays as a predisposing factor for the development of poststernotomy infections remains unconvincing. Studies by Crabtree and De Paulis show that female sex play a significant role in superficial wound infections, but not in DIS. Meta-analysis from 2016 (Balachandran et al.)

demonstrates the fact that women have a significantly higher incidence of complications than men regarding both superficial and deep wound infections. Interesting is the study of Copeland et al., who found an increased risk of wound complications in women with large breast size (macromastia). According to the authors, the large weight of unsuspended breasts causes inferolateral tension to the sternotomy wound and contributes to dehiscence with subsequent infection. According to Borger, on the other hand, male sex is an independent risk for DIS in patients who have undergone an isolated CABG procedure and postulate that due to the greater circumference of the chest wall in men, the tension in the wound area increases. In the patients studied in our institution, the ratio of men: women is 2:1 in DIS and superficial infections, and in SCF the ratio is 1:1. Probably the reason why men develop infections more often lies in the fact that they are more often affected by atherosclerotic heart disease than women, and coronary surgery accounts for over 50% of the clinic's interventions.

Studies examining the link between poststernotomy wound complications and smoking as a risk factor are limited. A recent meta-analysis did not show a significant association between smoking and DIS, although data is limited due to the small number of studies. Smoking disrupts the healing process of the wounds mainly due to reduced blood flow in the affected area, which results in tissue hypoxia. Moreover, cough, which is very often associated with smoking, also exerts tension on the sternal osteosynthetic wires, leading to rupture of the latter, sternal fractures and wound dehiscence. This mechanism is the reason why COPD is considered as one of the main risk factors for this type of complications. In the analysis of the risk factors in the studied patient population, the percentage of smokers is extremely high - 20.4% - in superficial wound infections, 22.8% - in SCF, 9.9% - in DIS. The percentage of patients with COPD is also high, as the disease is reported as a significant risk factor for the development of DIS and SCF - 15.3% and 14.3%, respectively. According to the CDC's recommendations, smoking should be discontinued at least 30 days before elective cardiac surgery. Other risk factors for wound infections include peripheral vascular disease, heart failure, renal failure, chronic infections, and prolonged preoperative hospital stay. They do not constitute a large percentage of the risk factors identified in our population and are reported as insignificant when they are the only risk factor. However, in combination with other risk factors, the cumulative risk increases. Patients with superficial wound infections, who had more than 1 risk factor, were 29.7%, with SCF - 22.9%, with DIS - 60.3%.

Perioperative implementation of preventive measures and interventions is the key to reducing the incidence of wound infections after open heart surgery. The latter should be aimed at reducing bacterial contamination of the wound and optimizing healing conditions. These measures include preoperative screening for nasal carriers of S. aureus, skin preparation, optimization of the

patient's premorbid conditions, antimicrobial prophylaxis, impeccable surgical technique.

Mediastinitis caused by MRSA is associated with a high 1-year mortality - up to 49%. Nasal carriage of S. aureus significantly increases the risk of developing infections by at least 3 times. All patients undergoing cardiac intervention should have negative microbiological results from nasal swab test or by polymerase chain reaction (PCR) testing, if possible (Class I Recommendation, Level of Evidence - A). Most heart surgical wound infections are caused by different types of staphylococci. Most of these infections result from the patient's own nasal flora. 20-30% of the total population are carriers of Staphylococcus aureus. Although only 5% to 15% of the patients admitted to intensive care units are carriers of MRSA, the risk of MRSA bacteremia postoperatively is significantly higher in these patients than the risk of bacteremia with methicillin-sensitive strains of S. Aureus (MSSA) in MSSA carriers. PCR analysis provides rapid screening (<12 hours) for staphylococcal carriers. However, the analysis increases costs and is not available in all hospitals. This, unfortunately, is the main reason why it is not applied as a standard practice in our institution. At the start of the program to reduce the rate of wound infections in the cardiac surgery clinic, nasal swab tests are taken routinely in all patients and in case of a positive sample patients are treated with nasal mupirocin. Intranasal mupirocin leads to immediate decolonization of MSSA in over 90% of cases. However, in patients with MRSA, therapy results in decolonization in only 45% to 50% of them.

Preoperative bathing with antiseptics is often used in cardiac centers to reduce bacterial colonization. Washing the body with a solution of chlorhexidine can be helpful in reducing the number of bacteria on the skin (Recommendation Class IIb; Level of Evidence - B). Although chlorhexidine reduced the number of bacteria on the skin to a greater extent than other agents, in three randomized, controlled studies, the authors did not find a significant difference in the rate of postoperative infections among patients, treated with a solution of chlorhexidine, povidone-iodine, soap and water, or placebo.[K-3] Kuhme et al. isolated CoNS and Propionibacterium acnes from subcutaneous tissue in 89% and from the skin around the incision area in 98% of patients who had been treated preoperatively with chlorhexidine. The authors conclude that skin preparation with chlorhexidine alone cannot prevent microorganisms from the skin flora and surrounding tissue from contaminating the wound during cardiac surgery, but reduces bacterial counts. In the light of current evidence, the 2017 recommendations of the European Association of Cardiothoracic Surgery (EACTS) are to bathe patients with soap either the day before or on the day of surgery (Class IIa, level B). On the other hand, the recommendations of the American Association of Thoracic Surgery (AATS) from 2016 suggest that chlorhexidine should be used to reduce the microbial count of the skin (class IIb, level B). Hair removal in the area of the surgical incision is best done

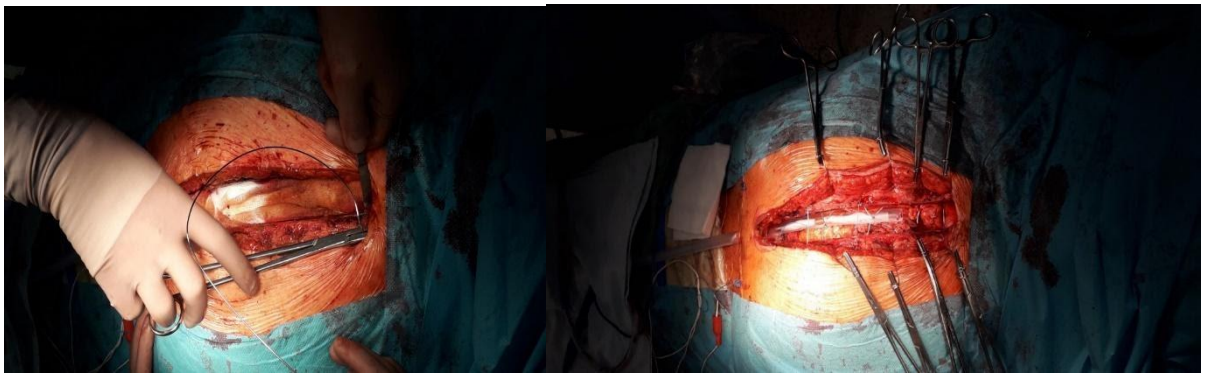
immediately before surgery instead of the night before to reduce the risk of wound infections. Cutting of the hairs is preferable to shaving or using depilatory products. The use of povidone-iodine or chlorhexidine is recommended for preparation of the operative field immediately before the incision and the present recommendations do not indicate a preference for any of the solutions. We have adopted the use of chlorhexidine solution and hair trimming in all patients immediately before surgery as part of a protocol of measures to reduce infections at the surgical site.

Antibiotic prophylaxis in cardiothoracic surgery undoubtedly plays an important role in the prevention of poststernotomy infections. Its importance has been clearly demonstrated in a number of placebo-controlled studies showing an approximately 5-fold reduction in postoperative wound infections. Various surgical associations recommend preoperative AB prophylaxis as standard practice in cardiac surgery. However, there is still considerable debate about the choice of medication, time, dose and duration of AB prophylaxis. In 2006-2007, STS published recommendations for the duration and choice of AB in cardiac surgery. The following is a summary of these recommendations. Cephalosporin - cefazolin or cefuroxime, should be administered intravenously within 60 minutes before the skin incision and should be continued for no longer than 48 hours (Class I Recommendation; Level - A). Dosage based on the patient's body weight is recommended and re-dosing is indicated for procedures longer than 4 hours. Vancomycin is reserved for patients with a history of type 1 allergic reactions to β-lactam agents or in cases with evidence or suspicion of MRSA (Class IIa Recommendation; Level - B). MRSA should be suspected in patients hospitalized for more than 3 days, patients transferred from other wards, procedures involving implantation of a pacemaker, cardioverter-defibrillator, intracoronary stent or stent in other peripheral arteries in institutions known to have a high prevalence of MRSA. Vancomycin is not recommended as a mono prophylactic agent in cardiac surgery (Class III Recommendation; Level B). Unlike β-lactam antibiotics, vancomycin has a narrower antimicrobial spectrum, less tissue and bone penetration, and a slower bactericidal effect than cephalosporins. The activity of vancomycin is essentially limited to gram-positive bacteria, especially MRSA. A gram-negative antimicrobial agent should be added when vancomycin is used as the primary prophylactic AB (Recommendation IIb; Level - C). In patients with beta-lactam allergy, vancomycin is considered the best AB for MRSA prophylaxis, but there are concerns about its lack of gram-negative coverage. Therefore, the addition of an aminoglycoside, usually gentamicin or other suitable antimicrobial agents (amikacin, tobramycin), is recommended. The combination of vancomycin and aminoglycoside has been shown to be associated with nephrotoxicity, ototoxicity, and delayed excretion after cardiopulmonary bypass. Therefore, the dose should be adequately reduced to avoid adverse reactions. The duration of postoperative AB prophylaxis should

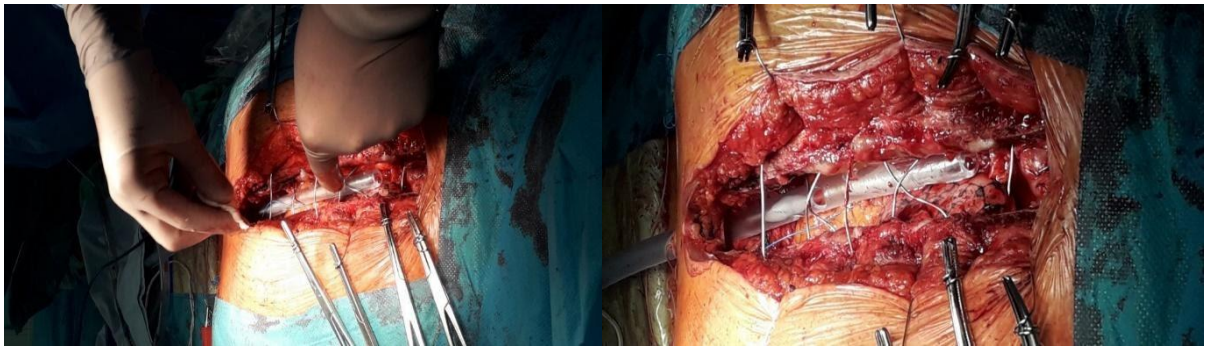
not exceed 48 hours (class IIa, level B). Long-term AB therapy has been associated with drug toxicity, the emergence of resistant bacterial strains, Clostridium difficile infection and increased healthcare costs. Lador et al. demonstrated in a meta-analysis that a duration of AB prophylaxis in the postoperative period of less than 24 hours was associated with a higher risk of wound infections, but a duration of more than 48 hours did not lead to an additional benefit. Mertz et al. also found that AB prophylaxis for more than 24 hours postoperatively reduced the risk of wound infections by 68%, although the meta-analysis was limited by the heterogeneity of the different antibiotic regimens in the published studies. Hamouda et al. reported a reduction in AB resistance and health care costs without an increase in the percentage of wound infections while reducing the duration of AB prophylaxis postoperatively from 56 to 32 hours. In our institution we apply cefuroxime 30-60 minutes before the skin incision in all patients. For those at risk and those with suspected MRSA, vancomycin is added 90 minutes before the incision to ensure sufficient MIC of the AB during the intervention. For procedures lasting more than 4 hours, a second dose of AB is administered. The duration of prophylaxis is applied postoperatively up to 48 hours or until the removal of the mediastinal drainage. Topical administration of AB to the edges of the sternum prior to osteosynthesis has been shown to significantly reduce the incidence of poststernotomy infections. In a prospective, randomized study that includes 416 patients with median sternotomy, Vander Salm et al. demonstrate that topically applied vancomycin significantly reduces the incidence of wound infections from 3.6% to 0.5%; P = 0.02. Lazar et al. in a retrospective, nonrandomized, single-center study involving over 300 patients who underwent open heart surgery, found that topically administered vancomycin (2.5 g in 2 ml saline) as a suspension at the edges of the sternum, together with strict glycemic control, resulted in complete elimination of superficial wound infections (0% vs. 1.6%; P <0.001), DIS (0% vs. 0.7%; P = 0.005) or other type of wound infections in non-diabetic (0%vs.2.2%);P <0.0001) and in diabetic patients (0%vs.3.3%; P= 0.0004). They also found that serum vancomycin levels returned to baseline on the sixth postoperative day. The authors emphasize that topical administration of vancomycin is not associated with an increased incidence of AB-resistant infections and does not lead to postoperative nephrotoxicity. In a retrospective study involving over 1000 patients, Arruda et al. managed to reduce the incidence of surgical site infections to 0.5% by using vancomycin paste. Gentamicin-collagen sponges have also been shown to significantly reduce the incidence of wound complications. Kowalewski et al. show in a meta-analysis that gentamicin sponges significantly reduced the incidence of both superficial and deep wound infections by 40%. In addition, they note that non-compliance with the manufacturer's recommendations to limit exposure to gentamicin sponges in saline prior to implantation between the sternal edges leads to lower gentamicin concentrations and this is the reason for the poor results of a

previous Bennett's study. In the light of current evidence, AATS guidelines recommend the use of local AB at the edges of the sternum prior to osteosynthesis (Class I, Level B).

The increase in the frequency of wound infections in our institution in the recent years has necessitated the search for new alternative techniques for the prevention of these potentially fatal complications, including the topical application of AB. The new surgical wound closure protocol was administered to 300 patients without allergies to vancomycin or gentamicin. This practice continued after the observation period described in the present analysis. Vancomycin paste is prepared as 3 grams of the antibiotic is mixed with 3-4 ml of saline, the suspension is mixed with an instrument to obtain a hard texture that is very similar to hemostatic wax. In patients with more severe bleeding from the sternum, vancomycin paste is mixed with hemostatic fibrillar - Surgicel® Fibrillar Absorbable Hemostat (Ethicon). It is applied directly to both sternal edges just before osteosynthesis.



A



B

C D

Figure 3: *Stages of the preparation of vancomycin paste and surgical technique for applying vancomycin paste in sternal osteosynthesis; A - Standard imposition of osteosynthetic bodies; C - Applying vancomycin paste on both halves of the sternum; C - The wires are tight and at this point the irrigation of the tissues with gentamicin solution follows; D - The operative wound is closed.*

Gentamicin solution is prepared by diluting 3 ampoules of the AB (240 mg) with saline to 10 ml. The subcutaneous tissues are irrigated with this solution after the sternum has been osteosynthesized, just before the subcutaneous sutures are applied. This step is added to the application of vancomycin paste due to the rare clinical application of gentamicin, which determines its high antibacterial activity after topical application. 8 (2.7%) of Group I patients developed superficial wound infections and only 1 (0.3%) patient developed deep sternal infection, which is significantly different from the results of Group II patients where superficial and deep wound infections occur respectively in 21 (7%) and 8 (2.66%) operated. In contrast to 2017, when the peak of wound infections was registered - 8.99% superficial infections and 2.80% DIS, for 2018 more than 50% reduction in the incidence was reported - 4.12% ($P = 0.0003$) for superficial wound infections and 1.28% ($P = 0.0488$) for DIS. There is no registered case in which complications have occurred or side effects related to the local application of AB in our clinic. Our results are comparable to previous reports on the protective effect of topical application of vancomycin and gentamicin separately, but the results of such a combined approach have not been reported so far. The local application of AB has been the subject of intense discussions in the recent decades. The method guarantees higher local concentrations of AB compared to systemic application, which results in greater efficiency. However, local AB is a potential risk factor for developing AB resistance. The present dissertation does not aim to discover AB resistance. Therefore, long-term negative effects may become apparent in the future.

Hemostatic bone wax acts as a foreign body and has been shown to adversely affect the healing of the sternum. In addition, it reduces the ability of bones to clear bacteria and has been found to be an independent risk factor for sternum dehiscence and poststernotomy infections. On the other hand, there is no evidence that its use is associated with reduced risk of bleeding or the need for blood transfusions. From the beginning of 2018, with the initiation of the

new protocol for prevention of wound infections, hemostatic wax is not used in our institution.

Good surgical technique is crucial for the prevention of wound infections. The skin incision should be gentle - starting a little above the angulus sterni and ending a little above the processus xiphoideus, which causes a more gentle opening of the sternal retractor. It is desirable to use a wide retractors to reduce the risk of sternal fracture. After the sternotomy, the sternum should not be manipulated with the hands, but only with instruments. Basic surgical techniques should be followed, which include hemostasis, limiting the use of diathermy, and careful surgical dissection to avoid excessive tissue injury.

Because processus xiphoideus is a cartilaginous non-vascularized portion of the sternum, as an alternative to total median sternotomy, a xyphoid-sparing sternotomy can be performed, and this technique has been shown to reduce the risk of DIS. Closing a sternum with multiple fractures using the Robicsek technique could prevent dehiscence and poststernotomy infections (recommendation IIa; Level = B). In a large retrospective study involving obese patients (BMI> 30 kg/m^2), the technique showed superiority over conventional closure methods, with a reduction in infectious complications of 6.15% to 0%. In another randomized study involving 815 patients undergoing median sternotomy, the Robicsek technique resulted in a reduction in the incidence of sternal dehiscence from 3.7% to 2.5%, although this proved to be statistically insignificant. In our institution, in cases with multiple sternum fractures, in patients with BMI> 30 kg/m^2 and in women with macromastia Robicsek's technique is applied.

Postoperative measures for the prevention of superficial and deep wound infections are of great importance. There are several important factors that could contribute to increasing the incidence of these complications. Retained coagulum in the pericardium is an ideal environment for the development of microorganisms, therefore every surgeon should perform adequate and thorough hemostasis to avoid re-exploitation of the mediastinum, which is an independent risk factor for the development of DIS. This is proved in the analysis of risk factors in the present dissertation. Early extubation can also reduce the incidence of surgical site complications, as well as early removal of urethral and central venous catheters. In our institution, the latter are removed on the 2nd postoperative day when the patient is transferred from the intensive care unit, if the medical condition allows it. The rehabilitation program for the patients from Group I of the study for the preventive measures has also been modified, and after the end of the period of observation of the scientific work, the program is accepted as a routine protocol in the clinic. Postoperative rehabilitation includes an individualized scheme for early rehabilitation of the patients, which depends on the heart status and the condition of the musculoskeletal system. Physical exercise increases gradually. Patients are taught how to properly perform daily

activities - getting out of bed, lying down, carrying weights and other activities as suggested by Adams et al.

The identification of biomarkers that provide evidence to support a clinical outcome has significantly influenced the development of medicine, helping clinicians in many specialties to predict the course of a disease. Numerous studies have found biomarkers that can be used as predictors of the status of patients after cardiothoracic surgery, and applications are numerous. In the present dissertation the preoperative values of troponin, CK, CK-MB, Pro-BNP and hs-CRP are analyzed. Troponin, CK, CK-MB, ALT, AST, lactate, CRP and PCT were measured 24 hours after the intervention. The aim is to determine which of them are potential biomarkers for the development of superficial and deep wound infections. Cardiac surgery elicits an inflammatory response involving clinical and biological changes in the body. SIRS is the result of multiple stimuli - contact of the patient's blood with non-physiological surfaces, surgical trauma, myocardial ischemia/reperfusion and release of endotoxins. Because of this response, conventional clinical and biological signs may be misleading in the diagnosis of postoperative complications, especially infectious ones.

Creatine kinase is an enzyme expressed by various tissue and cell types. It is a marker for myocardial damage used to diagnose acute myocardial infarction. In recent years, the test has been replaced by the troponin test.

A major cardiac biomarker is serum cardiac specific troponin T. TnT levels have been shown to correlate with the duration of cardioplegia. A new highly sensitive and specific immunoassay for the detection of cardiac troponin T in serum has recently been introduced into clinical practice. A promising and potential application for this marker is a more accurate prediction of the outcome of the patient's treatment and a clearer understanding of the extent of myocardial damage. As noted above, administration of cardioplegic solution carries potential risks, with some patients being able to endure longer periods of cardioplegia than others before adverse effects occur. After open heart surgery, the troponin test is an indicator of myocardial damage during the intervention (perioperative myocardial infarction). Troponin is increased in about 40% of patients with critical conditions such as sepsis. In these patients there is an increased risk of mortality and prolonged stay in the intensive care unit.

Pro-BNP is a heart hormone that is released by cardiomyocytes in response to ventricular dysfunction. Once discovered and described, Pro-BNP finds application mainly in the field of cardiology. Its prognostic value in cardiac surgery has been assessed in only a very small number of studies. The main goal of our study is to assess the factors that affect the level of Pro-BNP and its prognostic value. In a 2013 study by Liu et al., which included 225 patients after open heart surgery, the authors demonstrated a strong correlation between preoperative serum Pro-BNP concentration and postoperative mortality, with a limit of 2773.5 pg/ml (sensitivity 63, 6% and specificity 80.8%).

Lactate is an anion resulting from the dissociation of lactic acid, a product of glucose metabolism, in particular it is the end product of anaerobic glycolysis. Hyperlactatemia accompanied by metabolic acidosis in patients with systemic hypoperfusion and tissue hypoxia is common. Hyperlactatemia is a well-known marker of circulatory failure and is associated with mortality after heart surgery. Elevated serum lactate levels both during surgery and in the intensive care unit are associated with a poor prognosis. Low cardiac output before and during surgery is considered to be the most important cause of insufficient oxygenation and thus increases serum lactate levels. Its concentration above 3 mmol/L is considered an indicator of an increased risk of developing cardiovascular, infectious complications (mediastinitis) and mortality.

C-reactive protein (CRP) is a pentameric protein found in blood plasma whose circulating concentrations increase in response to inflammation. In the presence of a stimulus, the CRP concentration may increase to 500 mg/L in 6 hours and peak in 48 hours. The plasma half-life of CRP is 19 hours and is constant in all medical conditions. Therefore, the only factor that affects the concentration of CRP in the blood is its rate of synthesis, which increases with inflammation, infection, trauma, necrosis, malignancy and allergic reactions. In patients who underwent open heart surgery with CPB, an increase in CRP values was observed as a consequence of the immunomodulatory effect of ECC. According to numerous reports, CRP is a predictive marker for the development of mediastinitis after cardiac surgery. Very few studies have analyzed the effects of preoperative CRP measurement on postoperative outcome. They show that these patients have a higher incidence of postoperative infections, including superficial and deep wound infections. However, the role of preoperatively measured CRP values and those measured in the early postoperative period outcome in patients undergoing cardiac surgery remains unknown. In a study by Cappabianca et al. (2006), the authors demonstrated that a preoperative CRP level of 0.5 mg/dL or more is an independent risk factor for nosocomial death in 597 cardiac surgery patients. Fransen et al. demonstrate that CRP in excess of 0.8 mg/dL preoperatively, diabetes mellitus, and ECC time greater than 112 minutes are independent risk factors for the development of poststernotomy infections.

After decades of numerous studies and various attempts to analyze inflammatory markers after cardiac surgery, it is probably time to standardize the assessment of inflammatory status before and after cardiac surgery. Procalcitonin may play such a role. PCT is a 116-amino acid peptide secreted by parafollicular thyroid cells as a precursor to calcitonin. In terms of the inflammatory response, PCT is synthesized in almost all organs such as the liver, lungs, kidneys, intestines and almost all other tissues in the body. PCT production can be induced by gram-negative bacterial endotoxins or by inflammatory cytokines (e.g., IL-1 and IL-6 or TNF-α). High levels of serum PCT strongly correlate with the degree and severity of bacterial infections and

in cases of SIRS. The use of ECC in cardiac surgery results in varying degrees of SIRS, which is associated with an increase in PCT levels within the first 24 hours postoperatively, although a Boeken report suggests that ECC has no effect on PCT. PCT has been found to be elevated in infectious complications following open heart surgery, including wound infections, and plays an important role in their diagnosis and decision-making for further therapeutic concepts. However, these studies did not focus on patients with an initially uneventful postoperative course. The predictive value of elevated first postoperative day PCT levels in patients with initially uneventful postoperative course is still unknown. Our prospective study analyzed the predictive value in a single measurement of serum PCT to identify the risk of infectious complications, in particular wound infections, in patients after open heart surgery with an initially uneventful postoperative period. Despite the opinion that the single measurement of PCT has no special prognostic value, the present dissertation manages to prove the opposite. The most impressive conclusion from this study is that a single postoperative measurement of PCT levels predicts late complications in patients after cardiac surgery. Analysis of the data showed that 24 hours after the intervention, PCT levels were significantly increased in patients who later developed infectious complications. In terms of postoperative CRP levels and white blood cell counts, they proved to be insufficiently accurate indicators to distinguish those patients who would develop late complications from the rest. ROC analysis reveals the fact that postoperative serum PCT levels have the strongest prognostic value for the development of infectious complications. It can be concluded that PCT is a major predictive marker for the development of SIRS, sepsis, superficial and deep wound infections. It is more specific and more sensitive than CRP. PCT values above 2 ng/ml are associated with an extremely high risk of developing wound infections.

The other biomarkers proposed as a panel for potential predictive biomarkers proved to be statistically insignificant regarding the wound infections, but interesting conclusions can be drawn from their analysis:

- Elevated levels of CK-MB and Pro-BNP postoperatively are associated with the development of heart failure, myocardial damage, increased need for catecholamines and IABP implantation. These complications are risk factors for the development of wound infections;
- Preoperative serum Pro-BNP is a good prognostic indicator of outcome after cardiac surgery;
- Pro-BNP shows variability in patients undergoing cardiac surgery. Classification by NYHA, EF, pulmonary pressure, left ventricular enddiastolic volume, atrial fibrillation, preoperative plasma creatinine and cTnT levels correlated with preoperative Pro-BNP levels;

- Serum levels of Pro-BNP are a good predictor of complications after cardiac surgery and are comparable to euroSCORE and are a better marker than EF;
- Serum hs-CRP levels correlate with the occurrence of perioperative myocardial infarction in patients post CABG;
- Elevated lactate levels are directly related to in-hospital survival. Its concentration above 3 mmol/L is considered an indicator of an increased risk of developing cardiovascular and infectious complications (including mediastinitis) and mortality;
- CRP increases significantly after CPB, and values above 100 mg/L are predictors of the development of infectious complications.

The prevention of poststernotomy infections is multifactorial. Based on the observations and experience gained in the present study, as well as the recommendations of other authors on this serious surgical problem, we summarize the recommendations for minimizing surgical wound infections in Table 21. This is, in fact, part of the overall algorithm applied in our institution from the beginning of 2018.

Table 21: *Preventive measures for poststernotomy infections*

1.	Guarantee a minimum preoperative hospital stay the elective patients
2.	Treat all foci of extrathoracic infection, if the patient's heart status allows the delay of surgery
3.	Apply topical treatment with mupirocin in the absence of documented negative screening for Staphylococcus aureus infection
4.	Correct preoperative hypoalbuminemia if possible
5.	Smoking cessation and aggressive respiratory rehabilitation in patients with COPD
6.	Optimize serum glucose concentrations to less than 10 mmol/L in patients with poor glycemic control
7.	Preoperatively, the patient's hair is trimmed, not shaved; the body is treated with chlorhexidine solution immediately before surgery
8.	Administer cephalosporin intravenously within 30-60 minutes before the incision, second dose - in procedures lasting for more than 4 hours and not more than 48 hours. The dose should be determined according to the patient's weight
9.	Vancomycin should only be used in patients with a history of type I allergic reactions to β-lactam agents or in patients with isolated or suspected MRSA
10.	Do not administer vancomycin as a single prophylactic antibiotic for cardiac surgery
11.	Vancomycin should be administered intravenously 90 to 120 minutes before the skin incision and a maximum of only 1 additional dose when

	used with cephalosporins
12.	Add aminoglycoside 1 dose preoperative and 1 additional dose to cover gram-negative bacteria when vancomycin is the main prophylactic AB
13.	Apply a technique for harvesting a skeletonized internal thoracic artery in patients with diabetes and BITA
14.	Apply local AB (vancomycin paste + gentamicin solution) when closing the surgical wound
15.	Do not apply hemostatic wax for hemostasis of the sternal edges
16.	Apply the Robicsek technique in multiple sternum fractures and in patients with BMI> 30 kg/m^2
17.	PCT testing 24 hours postoperatively - if more than 2 ng/ml discuss AB therapy

Sternocutaneous fistulas are a rare but serious complication after open heart surgery. Due to their heterogenity, the latter are considered separately from superficial and deep wound infections. The frequency of SCF in the Clinic of cardiac surgery at the University Hospital "St. Georgi ``- Plovdiv for the period from October 2002 to June 2019 is 0.34%. Although there are few published studies on the frequency of SCF, the results presented are comparable to those of Steingrimsson and those in the Stoney's report. The lack of data on these complications is rooted in the fact that they remain poorly studied, although they cause severe deterioration in the quality of life. Another problem is the heterogeneous terminology used to describe the problem and its origin. Terms such as draining sinus, chronic sinus, chronic sternal osteomyelitis, delayed septic osteochondritis, and recurrent sternal infections have been used to describe SCF (Johnson et al., 1985; Pairolero et al., 1991; Petrikkos et al., 2001; Siegman -Igra et al., 1990; Stoney et al., 1978; Yuen et al., 1995). In our study, the strongest independent risk factors for SCF were diabetes mellitus, obesity, and smoking, with 19 (54.3%) patients having 1 risk factor and 8 (22.9%) having more than 1 risk factor. According to some authors, smoking is a major risk factor for the development of late infections. Peivandi et al. reported that age (over 75 years) was associated with the development of fistulas, which was not supported by our observations. Previous sternal infection is of great importance for the development of SCF. A total of 35 patients were examined retrospectively during the study period. 8 of them developed after treatment for DIS. Similar results were published by Jones et al. It is still debated whether previous DIS are really a risk factor directly related to the development of the SCF. A study by Steingrimsson supports the claim that there is no statistically significant relationship between the two diseases. SCF may occur de novo as a "foreign body" reaction in patients prone to infections, by analogy with other "foreign body" type infections such as prosthetic endocarditis and post-prosthetic infections. Previous reports suggest that SCF result from inadequate operative wound debridement in poststernotomy

infections, but it could also be suggested that these diseases have no clinical connection but rather have a similar risk profile. In our group of patients, the most commonly isolated microorganisms are CoNS and St. aureus. This fact could reinforce the hypothesis that SCF are a "foreign body" infection to steel wires for sternum osteosynthesis. Several publications have found that CoNS attaches to foreign materials and forms a biofilm leading to a low virulence infection with a protracted course. The immune mechanisms of the host patient are usually able to eliminate such infections, but in some patients, especially those who are immunocompromised, these reactions may be ineffective, leading to persistence of the infectious process. In addition, hemostatic wax can be considered as a foreign body, a possible source of low virulence pathogens, which may explain the finding that the use of bone wax during cardiac surgery is associated with wound complications. Sudmann et al. show that of the 18 autopsy cases of patients who underwent open heart surgery, 17 had evidence of chronic inflammation - even up to 10 years after primary surgery. In a rat model, the presence of bone wax in a sternotomy wound increased the risk of S. aureus infection, and in rabbits, bone wax was shown to prevent the union of the sternal edges compared to polymer. The treatment of SCF is complex and includes AB treatment according to the isolated microbiological causative agent and various surgical approaches. In the present dissertation we have retrospectively analyzed the results of the therapeutic regimens. Empirical therapy with cefuroxime, vancomycin or dalacin C is initiated. In 14 of the patients, SCF was treated with a single-step approach. The fistula is excised to vital surrounding tissues and deep to the sternum. All foreign objects visible in the area of excision (osteosynthetic wires, pacing electrodes, sutures) are removed. The wound is sutured. In other patients in whom computed tomography reveals osteomyelitis of the sternum, which is confirmed intraoperatively, the fistula is excised, bone sequesters are removed. Then a VAT system is installed. Many patients require several surgical revisions and all of them require long-term AB treatment. A number of surgical regimens for the complex treatment of this complication have been described (Falagas & Rosmarakis, 2006; Pairolero et al., 1991; Siegman-Igra et al. 1990; Johnson et al., 1985; Herrera et al., 1983). However, there is no consensus on the optimal treatment of late wound infections. The results achieved in our institution are comparable to the data presented in the literature. The average in-hospital stay is 22 days. There are no reported cases of in-hospital mortality. Recurrence of the disease is registered in 12 patients (34.3%), 7 were from the group treated with a one-step approach and 5 were from the group treated with VAT. They are rehospitalized and treated again. In 4 of the patients even more rehospitalizations are required.

There are many current options for treating superficial and deep poststernotomy infections. These include, but are not limited to, refixation with irrigation of antiseptic solution - conventional surgical technique, VAT, soft

tissue flaps implantation. The goal of modern surgical treatment is to perform a radical debridement of the affected area. This includes complete excision of all non-vital, infected and necrotic tissue components. Foreign materials, such as pacing wires must be removed. Continuing infection supports the process of necrosis, which then leads to tissue loss. Subsequent reconstruction procedures are doomed to failure. Reconstruction of the anterior chest wall can also be achieved by local pediculized or free flaps.

The success of the treatment of any wound infection is determined mainly by the early performance of debridement. In a retrospective study, patients in whom the wound was re-explored on the day of diagnosis had a shorter hospital stay than those in whom surgical treatment was delayed for more than 7 days after diagnosis. Titanium plate fixation of the sternum is also gaining popularity as part of many therapeutic regimens.

Treatment of superficial infections includes wound opening and drainage to allow unobstructed drainage of purulent contents, debridement, and regular sterile dressings. In addition, VAT is also used in these conditions. In the present dissertation the methods of treatment of superficial wound infections, as well as the achieved results, correlate with the reports presented in the literature. The therapeutic strategy includes AB treatment, wound debridement, and daily sterile dressings. Empirical therapy with cefuroxime, vancomycin or dalacin C is initiated. Once a microbiological agent has been identified, AB treatment is consistent with antibiotic data. In 27.8% (177 patients) VAT was installed. In 419 (65.8%) of the patients a secondary suture of the operative wound was performed without prior application of VAT, and in the others the wound healed secondarily. The average hospital stay of patients is 13 days. There are no reported cases of in-hospital mortality. 1 died 4 weeks after discharge from intracerebral hemorrhage. Two of them, treated without VAT, developed deep wound infection of the sternum, which required rehospitalization and treatment of DIS. Cicatricial necrosis is observed in 60 of the patients (9.42%).

Deep wound infections are significantly more difficult to treat, and the associated mortality is much higher than superficial wound infections. There is currently no general consensus on appropriate postoperative surgical therapy for mediastinitis/osteomyelitis of the sternum. The search for standardized treatment for this complex and important cardiac surgery problem is still ongoing. DIS therapy should be individualized, as noted earlier, but the principles are standard. These include removal of all devitalized and necrotic tissues, drainage of all infected areas, AB therapy, elimination of "dead spaces" and techniques for stabilizing the chest wall. After sternal debridement, the wound may be closed immediately or in a second stage. Immediate refixation can be performed if the deep mediastinal tissues are free of infection, there is enough tissue to ensure stable osteosynthesis, and the patient is clinically stable. In those cases where closure of the sternum is possible but there is still a mediastinal infection, refixation with irrigation of the mediastinum is the

method of choice. In addition to open and irrigation techniques, combined procedures could be applied, which are assessed individually in each case. The conventional irrigation surgical technique replaced the daily dressing change of the open technique when it was first developed in 1963. This idea of closing the sternum is revolutionary, as it eliminates the instability of the chest associated with secondary wound healing and eliminates the need for prolonged intubation and immobilization. Bryant et al. advocate for the addition of AB to the irrigation solution. Grossi et al. followed up 77 patients with DIS treated by irrigation with AB solution. When applied within 3 weeks of the primary intervention, treatment success was 90% with an overall mortality of 22%. Currently, in most surgical centers, as in our case, irrigation is performed with a solution of povidone-iodine. However, it is clear that regardless of the type of irrigation solution, the benefits are evident in the first 2 weeks of the clinical signs of mediastinitis. Delayed clinical presentation or long-term infection will not be positively affected by applying this method. However, animal experiments show that the systemic absorption of iodine in this method is extremely high. This is associated with complications such as renal failure, electrolyte changes, iodine metabolism disorders, thyroid dysfunction, cardiac arrhythmias, changes in mental status and seizures. This is the reason why many surgeons prefer alternative methods of treating DIS, although in our group I - 61 patients treated with irrigation and refixation, such complications were not registered due to the short period (<72 hours) of iodine irrigation. In this group we registered therapy failure in 5 patients, which required re-intervention - VAT and rerefixation.

Acute, subacute and chronic wounds are characterized by more or less soft tissue swelling, which can impede lymphatic drainage and microcirculation. The vacuum systems remove the exudates, which reduces the pressure in adipose tissue. This leads to dilation of the capillaries and improvement of blood flow, followed by proliferation of granulation tissue and neoangiogenesis. The number of bacteria decreases due to the continuous removal of secretions and debris. Sjögren recommends this procedure as a stand-alone treatment with direct closure of the sternum and soft tissue layers, and most surgeons use it as a transitional procedure as short as possible until final recovery with a muscle flap. The wound dressing should be changed every two to four days, taking samples for microbiological examination and, if necessary, performing a necrectomy. The frequency of dressing changes is dictated by CRP levels, as the change is performed under general anesthesia or sedation and the rules of asepsis and antiseptics are strictly followed. The wound is considered "clean" if the following requirements are met:

- there is a decrease in inflammatory markers (CRP in the range of 30 to 70 mg/l, leukocytes, fever, PCT) and no evidence of infection in another part of the body (eg pneumonia);
- there are at least two negative microbiological samples.

In addition, visual inspection must demonstrate:

- well-vascularized wound covered with granulation tissue;
- missing or minimal wound secretion;
- missing or minimal areas of the wound with necrotic tissue.

In the presence of these conditions, reosteosynthesis of the sternum can be performed and the wound can be closed. Numerous reports reveal excellent results with the use of VAT in poststernotomy infections. Tang et al. describe in detail the complete healing of osteomyelitis of the sternum, applying this method. In fact, Cacyi et al. demonstrate the link between VAT and improved survival in patients with mediastinitis. This finding is further supported by Baillot, who reported a 15-year follow-up of nearly 25,000 sternotomies and noted a significant difference in early and long-term survival. Gdalevitch et al. found that in patients with negative blood cultures, wound depth less than 4 cm and low degree of sternum instability, vacuum therapy was 100% successful. In our study, VAT was applied to 68 patients (Group II). Re-intervention is required in 7 of them. In 3 - VAT and refixation, in 4 - omentoplasty (in 2 and titanium plate implantation). Complications associated with VAT are usually minor. The main complaints of patients include pain at the edges of the wound, which usually subsides shortly after the initiation of negative pressure. The internal growth of young granulation tissue in the foam or gauze strips can also cause slight bleeding when they are removed when changing the dressing. Preventable complications of VAT include decubitus injuries caused by pressure from the drainage tubes to the skin and necrosis of the wound edges if polyurethane foam or gauze strips are placed outside the wound surface on healthy skin. The most serious and only potentially fatal complication of using a vacuum therapy system is massive bleeding, which occurs with a rupture of the right ventricle or bypass graft (in patients post CABG). This dramatic complication was fatal in two of the Group II patients. Studies have shown that rupture of the right ventricle is more likely to occur in patients with wound infections treated with VAT than conventional methods. This is explained by the displacement of the heart to the sternal edges, a result of the negative pressure created. Kiessling even described a case of rupture of the ascending aorta by an osteosynthetic wire.

VAT shows promising results in both the short and long term compared to conventional techniques. Two independent studies, one retrospective by Sjögren et al., which describes 101 patients with DIS and the other, a retrospective study by Deniz et al., which includes 90 patients with DIS, show significantly lower 90-day mortality. and treatment failure in patients treated with VAT compared to those treated with conventional techniques. The cause of all deaths was multiple organ failure as a result of severe sepsis. Both studies showed increased overall survival in the VAT group. De Feo et al. examined 157 patients in a retrospective study and found reduced mortality after VAT compared with conventional treatment. They also report lower levels of

reinfection. On the other hand, a retrospective study by Risnes et al., which examines 130 patients with poststernotomy infections, found no significant difference in long-term survival between patients with VAT and those treated with closed irrigation. However, the risk of sternal wound reinfection was higher in the closed irrigation group. Meta-analysis of Damiani et al. of 321 patients did not show significant differences in mortality between VAT and conventional therapy. Another retrospective study by Sjögren et al. shows that patients with DIS treated with VAT have similar long-term survival in patients without mediastinitis post CABG. Contradictory results have also been published regarding the length of hospital stay and the duration of treatment. Dos et al. describe a retrospective study demonstrating a shorter length of hospital stay in post-VAT treatment compared to conventional treatment. These results are supported by a retrospective study by Simek et al., a meta-analysis by Damiani and a retrospective study by De Feo. On the other hand, no significant differences were observed in the length of hospital stay or duration of treatment between VAT and closed drainage with irrigation in the two studies conducted by Sjögren and Deniz mentioned above, as evidenced by our observations.

Table 22: *Comparison between VAT and refixation with irrigation, according to different authors*

Author	**Follow-up**	**Number of patients + method of treatment**	**Results**
Berg	Retrospective	31 - VAT 29 - irrigation	VAT - lower risk of treatment failure and (52 vs. 16%, $p < 0.05$) and shorter hospital stay (6.9 vs. 6.6%, NS)
Doss	Retrospective	22 - VAT 22 - irrigation	VAT - shorter hospital stay (27.9 ± 6.6 vs. 33.0 ± 11.0 days, $p = 0.03$), no significant difference in mortality
Song	Retrospective	18 - VAT 17 - irrigation	VAT - shorter hospital stay (6.2 vs. 8.5 days, $p < 0.05$), no significant difference in mortality (11 vs. 6%, NS)
Luckraz	Retrospective	27 - VAT 13 - Irrigation	VAT - lower risk of treatment failure (15 vs. 30.7%, $p < 0.05$), lower mortality (7.5% vs. 18.5%, $p < 0.05$)
Fuchs	Retrospective	35 - VAT	VAT - leads to faster wound

		33 - irrigation	decontamination (16 vs. 26 days, p <0.01), shorter hospital stay (25 vs. 34 days, p <0.01)
Sjoegren	Retrospective	61 - VAT 40 -irrigation	VAT- lower risk than no therapy success (0 vs.15%, p <0.01), lower mortality (0 vs. 15%, p <0,01)
Immer	Retrospective	38 - VAT 17 - irrigation	VAT - shorter hospital stay (51.5 ± 20.8 vs. 70.7 ± 28.8 days, p <0.05), with no significant difference in mortality (5.3 vs 11.8, NS)
Segers	Retrospective	29 - VAT 34 - Irrigation	VAT - lower risk of treatment failure (27.6 vs. 58.9%, p <0.05), with no significant difference in mortality (3.5 vs. 2.9%, NS)
Petzina	Retrospective	69 - VAT 49 - irrigation	VAT - lower risk of treatment failure (2.9% vs.18.3% p <0.05), lower mortality (5.8% vs. 24.5% p <0.05), with no significant difference in hospital stay (38 vs. 41 days, NS)
Assman	Retrospective	69 - VAT 49 - irrigation	VAT - shorter hospital stay (45.6 ± 18.5 vs. 55.2 ± 23.6 days, p <0.05), lower mortality (14.6 vs. 32.4%, p <0.05)
Deniz	Retrospective	47 - VAT 43 - irrigation	No significant difference in risk of treatment failure (2.1% vs. 4.7%, NS), no significant difference in hospital stay (18 ± 9 vs. 24 ± 10 days, NS),
Raja	Meta-analysis	13 articles focused on comparing VAT with irrigation	No significant difference in risk of treatment failure and no significant difference in hospital stay
Schimmer	Meta-analysis	15 articles focused on comparing VAT with irrigation	VAT - lower risk of treatment failure, lower mortality. Routinely applied method of first choice in 35% of cardiac centers in Germany
Damiani	Meta-analysis	6 articles focused on comparing	VAT – shorter hospital stay, lower mortality

		VAT with irrigation	
Stoev et al.	Retrospective	61 – VAT 68 – irrigation	No significant difference in risk of treatment failure (8.2% vs. 10.3%, NS), no significant difference in hospital stay (15.43 vs. 16.53 days, NS)

Regardless of whether VAT or irrigation refixation is used, the most common method for sternal refixation in patients with mediastinitis and sternal dehiscence is reosteosynthesis with steel osteosynthetic wires in cases of sufficient residual bone tissue, which are applied in a manner similar to the initial surgical intervention or alternative techniques (*Robicsek)*. The correct placement of the osteosynthetic wires is extremely important in order to achieve a stable fixation. If the wires are placed incorrectly, the latter can cut and form bone sequesters. This is a major cause of early reinfections or late SCF.

Following osteomyelitis, the quality of the residual sternum and the lack of bone areas make re-imposition of osteosynthetic wires an extremely difficult and risky task for the cardiac surgeon. The development and occurrence of extensive and dense adhesions between the lower surface of the sternum and the heart in patients with mediastinitis increase the risk of injuring the right ventricle and bypass grafts in sternal bone when peri-, trans-, and parasternal techniques for reosteosynthesis are used. In recent years, more and more different types of metal (titanium) plates are used to achieve stable osteosynthesis. Voss et al. reported institutional experience with titanium plates from the Titanium Sternal Fixation system ™ in 15 patients with sternal dehiscence. Four of them had more than two previous attempts to stabilize the chest, using various techniques for metal osteosynthesis with steel wires. Four of the patients were treated for mediastinitis using VAT. All patients were successfully stabilized and discharged from the hospital in good health, except for one who died from a complication unrelated to metal osteosynthesis and titanium plate implantation. One of the patients in the group with mediastinitis developed a late recurrence of the infection. More experience with the same Titanium Sternal Fixation™ system has been reported by Baillot et al., who are treating a group of 92 patients after DIS. They achieved stability in all cases, but 9 of the patients (9.8%) had a late recurrence of the infection. Some of them required the removal of the titanium plate. Chest stabilization in DIS improves respiratory function, improves and accelerates the wound healing process, shortens hospital stay and improves the patient's quality of life. Titanium plate implantation seems to be an effective and reliable method of stabilizing the chest, but treatment may fail if there is massive bone loss. In these cases, the residual sternum does not allow a sufficiently reliable attachment of the plate or there is a large cavity between the bone segments. The mechanical stress that is

created in the area of the "neosternum" can loosen the screws or they can cut in the place of their grip, which poses a threat to the stability of the chest wall. In this case, patients often complain of constant pain and respiratory discomfort. The conventional surgical approach for sternal refixation does not provide good results when there is a large defect of the residual bone. This leads to unstable sternal osteosynthesis and even if an omental or muscular flap is applied to eliminate the "dead spaces", the approach does not give satisfactory results. Some authors report late infectious complications even if the wound appears to have healed well. In our clinic we have successfully integrated the construction of "neosternum" with titanium plates.

Reconstructive surgery with soft tissue flaps should be considered in patients with a significant defect of the sternum and soft tissues (class II, level B). This is usually done a few weeks after the initial operation. Factors such as location, extent of sternum involvement, and comorbidities of patients play an important role in determining the type of flap for reconstruction. The importance of early soft tissue flap plastics was emphasized by Lo et al., who found that a daily delay from diagnosis to coverage of the defect increased the risk of chronic infection by 1.2 times per day. In addition, Cabbabe et al. reported that patients with DIS who underwent an aggressive one-step wound debridement procedure and muscle flap application were associated with significantly lower mortality and complications, as well as shorter hospital stay than patients treated by multi-stage methodologies. Minchev in Bulgaria came to the same conclusions, applying one-stage omentoplasty with excellent results. Pedicled muscle flaps promote early wound closure and reduce mortality. In a follow-up of 211 patients with DIS treated with pectoral flaps, successful healing of the wound was achieved in 95% of patients with a mortality of 5.7%. Davison et al. in a retrospective study based on 130 patients, with 41 undergoing pectoral flap transposition and 56 with rectus muscle transposition plastics, concluded that m. rectus abdominis shows superiority over m. pectoralis major with respect to defects localized in the distal third of the poststernotomy wound. Omentoplasty is an extremely useful reconstructive option, as it is able to reach deep into the mediastinum and has immunological properties. Many reports demonstrate the superiority of the method over others in preventing septic conditions. Omentum majus has been used clinically to support wound healing and to stimulate revascularization of ischemic tissues. The mechanism that is biologically responsible for these effects has not yet been determined. A number of polypeptide growth factors that possess potent angiogenic properties have recently been identified. It is possible to identify one of them as a growth factor that may be responsible for the angiogenic properties of the intestinal mucosa. Vascular endothelial growth factor (EGF) levels in a number of rat tissues and organs were analyzed by enzyme and immunoassay. The omentum has been shown to have the highest concentrations of EGF. Studies of fractionated omentum also show that omental adipocytes, more than

stromal vascular cells, are a major source of EGF. The latter is a major angiogenic factor and is probably the reason for the omentum-induced angiogenesis. Increased EGF expression by omental cells under hypoxic conditions may reflect the mechanism responsible for increasing omental angiogenic activity in ischemia. It is precisely these qualities of the omentum, described by Zang et al., its plasticity, immune activity and resorption, that underlie the treatment of osteomyelitis and severe wound infections. Omentum majus is a well-vascularized tissue with abundant lymphatic drainage. Its dimensions reach 36x46 cm and are reliable for covering large defects. However, it is difficult to predict the size of the flap preoperatively because the size of the omentum does not directly correlate with the patient's habitus. The omentum can be transposed in different ways. If the thoracic defect is in the distal part of the poststernotomy wound, both gastroepiploic arteries (aa. Gastroepiploicae) are preserved in the pedicle of the flap, and in the case of a large defect the flap is mobilized together with one of the gastroepiploic arteries to cover the defect along its entire length. Passage of the omental flap from the upper-midline laparotomy through the subcutaneous tunnel to the sternum is associated with a risk of developing late postoperative hernias - 21%. Therefore, some authors recommend transposition through the transdiaphragmatic tunnel right to ligamentum falciforme. The risk of infection of the abdominal cavity is minimal, but the traction of the gastroepiploic artery can cause disturbances in the motility of the stomach and duodenum. The laparoscopic technique for harvesting the omental flap is associated with reduced pain syndrome and surgical site complications. The experience of our institution with soft tissue flaps is limited. In recent years it has become more and more common, but it is most often used in case of failure of the other treatment methods. As a primary therapy for DIS in 16 of the patients in Group III, a flap of omentum majus was used for chest wall reconstruction. In 1 patient in this group, anterior abdominal wall plastic surgery was performed using a polypropylene mesh (Ethicon) 4 months after surgery due to an epigastric postoperative hernia. M. rectus abdominis flap was used only in 1 patient - a woman aged 75 years post aortic valve replacement and CABG. She had a large soft tissue and bone defect. Osteomyelitis also affected IV costal cartilage, which necessitated its resection. The patient had a history for right mastectomy followed by chemotherapy and radiation therapy, as well as Wertheim operation. P. mirabilis was isolated from the wound sample. AB treatment and daily sterile dressings were initiated and continued for 9 days. After 2 consecutive negative microbiological samples, we proceeded to the reconstruction of the chest wall with a rectal flap in collaboration with a reconstructive surgeon. The technique consists in the following: the skin incision is continued distally until the desired length of the flap is reached. The skin is dug over the fascia to present the muscle. The anterior part of the fascia is then opened and the muscle is mobilized and cut.

The distal epigastric vessels are ligated and cut. The muscle then turns to the defect and is covered with skin.

Table 23 compares the results reported by different authors regarding the number of operated patients, perioperative mortality, hospital stay and complications.

Table 23: *Comparison of results (complications include AKI requiring CVVHDF, septic shock (MODS) and reinfection requiring omentoplasty)*

Author	**N**	**Mortality%**	**Method**	**Hospital stay**	**Complications**
Schroeyers	64	24	Muscle flaps reconstruction	24	12
Wouters	52	30.4	Refixation irrigation	48	5
Sherry	24	0	Irrigation fixation; Muscle flap reconstruction	66	10
Yasuura	44	16	Omentoplasty	18	22
Ascherman	20	5	Muscle flaps reconstruction; Omentoplasty	28	2
Pairolero	100	2	Muscle flaps reconstruction; Omentoplasty	30	30
Elawadi	34	0	VAT; Muscle flaps reconstruction	16	0
Sjogren	176	1.1	VAT; Muscle flaps reconstruction	28	2.3
Minchev	100	4	Omentoplasty	12	17
Stoev et al.	146	13.7	VAT; Fixation with irrigation; Omentoplasty	16	23.3

The same table is presented in the graph for clearer presentation of the data.

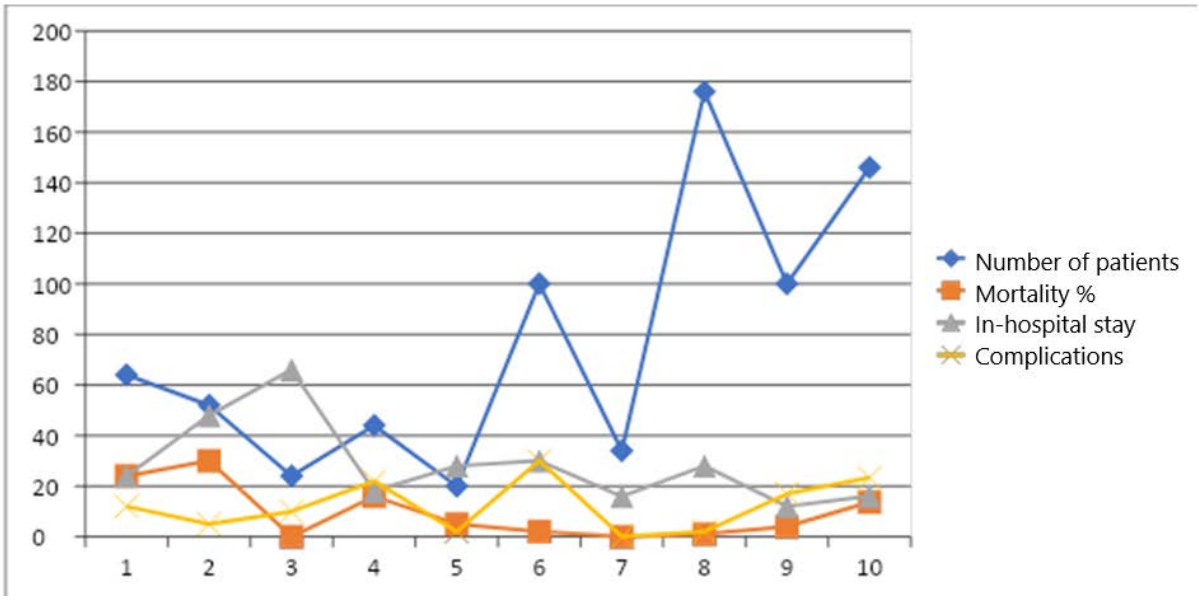


Diagram 23: *Graphical presentation of the comparison of the results*

A special impression in this table is made by the work of Jeffrey Ascherman, who operated on 20 patients with DIS and heart transplantation with very good results, using omentoplasty and myoplasty. The total frequency of DIS in the Clinic of cardiac surgery at the University Hospital "St. Georgi ” in this study is 1.42%, which is at the lower end of the range of values often cited in the literature, but the number of surgical interventions is close to the maximum. In terms of perioperative mortality after the applied methods of treatment, our results are comparable with other authors. This is also one of the main tasks in the treatment of these patients in the study. Authors with lower perioperative mortality have fewer patients.

In the category hospital stay we have achieved a good result compared to the data in the literature. This is achieved with correct, accurate and purposeful work of the team that cares for the patients. In the category complications, the percentage achieved in the present study correlates with the clinical severity of the operated patients with DIS.

Based on our observations, the experience gained in this area of the cardiac surgery, as well as the recommendations of other authors, we propose an algorithm (protocol) for the treatment of patients with superficial and deep wound infections (Figure 4).

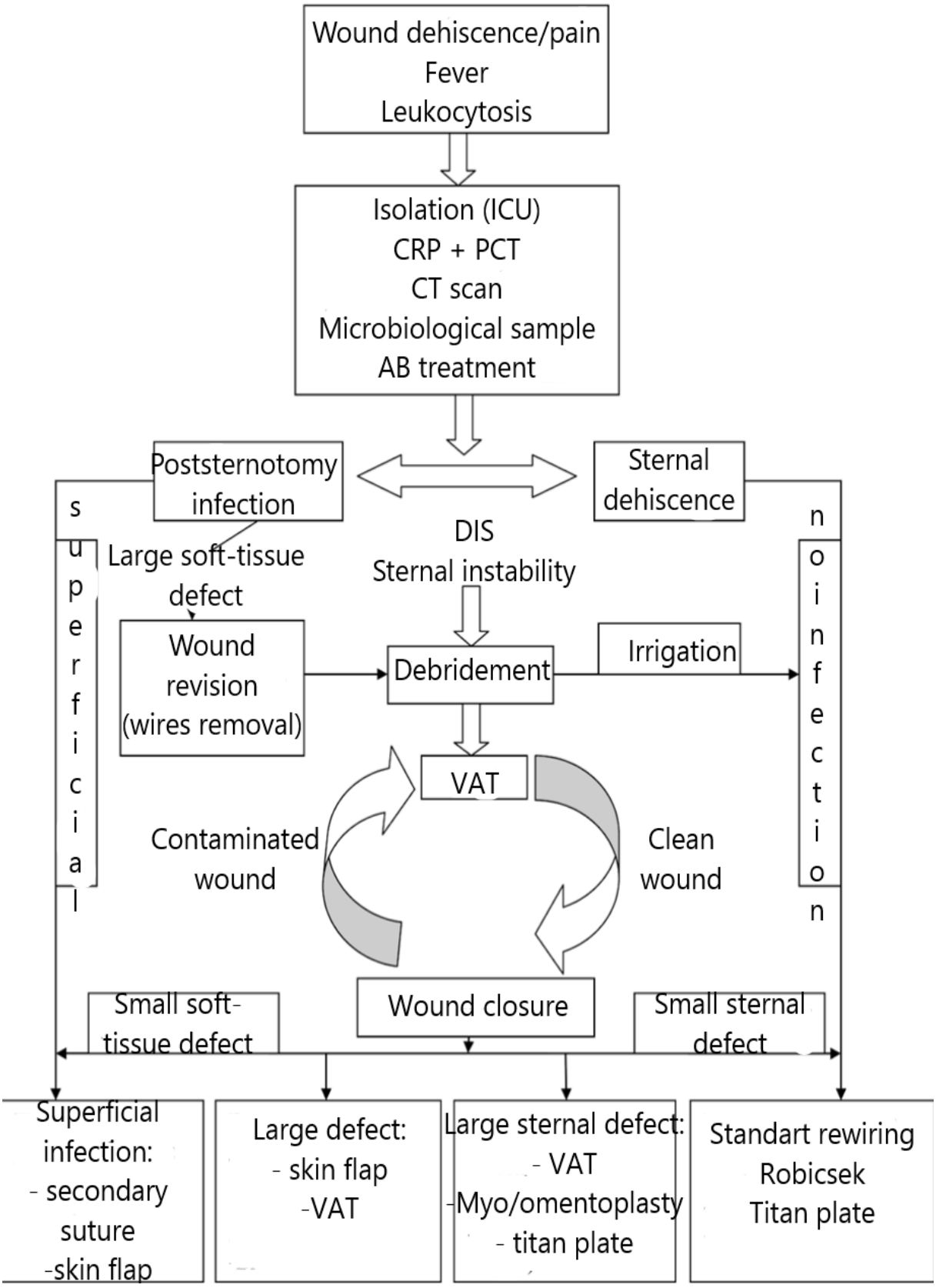


Figure 4: *Algorithm for behavior in poststernotomy infections*

6. Conclusion

Despite the great advances in medicine, superficial and deep wound infections and sternocutaneous fistulas remain a potentially fatal complication after open heart surgery, significantly increasing hospital stay and leading to significant financial costs for the health system. Strict perioperative glycemic control, proper surgical technique, administration of local AB, skeletonization of the internal thoracic artery, ensuring stable sternal osteosynthesis in high-risk patients, including diabetics, those with obesity, COPD, immunosuppressed, appear to reduce the risk of developing infections. Constant monitoring of these complications in the heart centers, such as ours, is imperative. In this way, both patient safety is guaranteed and the quality of care provided in the hospital is assessed. This includes recording of the main well-documented risk factors in patients with wound infections, monitoring compliance with treatment protocols, followed by meticulous follow-up. Early detection by PCT testing postoperatively leads to a rethinking of the AB strategy and could prevent their occurrence. With the advent of vacuum-assisted therapy, short- and long-term survival increases compared to open techniques. Titanium plates, with or without myoplasty or omentoplasty, provide stability to the chest wall even with significant bone loss. Future studies should focus not only on complications and mortality from poststernotomy infections, but also on the quality of life of the patients. It is important to pay attention to the methods for improving the outcome of the treatment of DIS, but the most important thing is their prevention. Although the population of cardiac surgery patients is becoming increasingly at risk - patients with higher EuroSCORE, polymorbid and requiring more comprehensive surgical treatment in the last decade, the incidence of mediastinitis has not changed. And despite the fact that most patients in the present dissertation have several risk factors, observations show that early therapy is associated with excellent survival and low failure rates. The prognosis of DIS may be influenced by the adequacy of the treatment.

7. Final conclusions

1. Microorganisms causing wound infections in our institution are similar to those described in other reports. CoNS and S. aureus are mainly isolated from wound samples - Gram(+); and A. baumanii, E. coli, and Kl. Pneumonia – Gram (-) bacteria.
2. The main antibiotic for the prevention of surgical infections is recommended to be cephalosporin first or second generation or another beta-lactam AB - cefazolin or cefuroxime. In high-risk and emergency patients, as well as in those with valve intervention, vancomycin is recommended as adjuvant AB. Mupirocin is recommended as a routine prophylactic measure for nasal carriers of S. aureus.
3. The incidence of wound infections in the clinic is similar to other cardiothoracic centers, with an incidence of 1.42% for deep wound infections, 6.18% for superficial wound infections and 0.34% for sternocutaneous fistulas over a 17-year period.
4. Sternocutaneous fistulas are a serious complication after open heart surgery. Patients with SCF require multiple hospitalizations and multiple surgical procedures. The clinical presentation and risk factors for SCF indicate that it is a "foreign body" type infection that occurs de novo, similar to prosthetic endocarditis in susceptible patients. The results of the treatment suggest that VAT may be a valuable adjunct to conventional surgical tactics.
5. There is a statistically significant upward trend for the studied seventeen-year period of the relative frequency in % of deep wound infections in relation to the number of open heart operations until 2017, as the main identified risk factors for developing post-sternotomy infections are diabetes, obesity, smoking and COPD.
6. The results from the application of different methods of treatment of mediastinitis - VAT with subsequent refixation, refixation with irrigation of antiseptic solution, omentoplasty indicate that there is no statistically significant difference in terms of hospital stay, complications and postoperative mortality.
7. Procalcitonin is a major predictive marker for the development of SIRS, sepsis, superficial and deep wound infections. It is more specific and more sensitive than CRP. PCT values above 2 ng/ml are associated with an extremely high risk of developing wound infections.
8. Pro-BNP shows variability in patients undergoing cardiac surgery. Classification by NYHA, EF, pulmonary pressure, left ventricular enddiastolic volume, atrial fibrillation, preoperative plasma creatinine and cTnT levels correlates with preoperative Pro-BNP levels.
9. Elevated lactate levels are directly related to in-hospital survival of patients. Its concentration above 3 mmol/L is considered an indicator of

an increased risk of developing cardiovascular and infectious complications (pneumonia, sepsis, mediastinitis) and mortality;

10. CRP increased significantly after CPB and values above 100 mg/L are predictors for the development of infectious complications.
11. Topical application of vancomycin paste along the edges of the sternum before osteosynthesis in combination with soft tissue irrigation with gentamicin solution is associated with a reduced risk of developing post-sternotomy infections.
12. This dissertation presents favorable immediate results (mortality, hospital stay, complications), which are comparable to most major cardiac surgery centers.

8. Contributions

1. The present dissertation presents the largest reported population of patients with superficial and deep wound infections and SCF after open heart surgery, analyzing the microbiological agents, risk factors and the results of different methods of treatment.
2. The study compares the results of the treatment of poststernotomy mediastinitis in different surgical tactics - vacuum-assisted therapy with subsequent refixation, wound debridement with subsequent refixation with irrigation of antiseptic solution and soft tissue flaps transposition.
3. For the first time in Bulgaria, renal replacement therapy with oXiris filter was applied in patients with septic shock and mediastinitis.
4. The surgical techniques for treatment of superficial and deep poststernotomy infections are visually presented.
5. For the first time in our country a technique for application of two local antibiotics for prevention of poststernotomy infections is described in detail.
6. For the first time in our country a technique for mixing vancomycin paste with hemostatic fibrillar for the purpose of hemostasis of the sternum has been described.
7. For the first time in our country a case of titanium plate implantation has been described, in combination with omentoplasty as a primary treatment of mediastinitis.
8. The predictive role of procalcitonin in the development of septic conditions was confirmed by assessing its predictive value.
9. A comprehensive algorithm for prevention and complex treatment of poststernotomy wound infections has been proposed.

9. Publications related to the dissertation

Publications:

1. Methods for prevention of wound infections in cardiac surgery. H. Stoev, D. Batashki. MU - Plovdiv. Savremenni medicinski problemi. Issue 4/2019, 19-22
2. Sternal reconstruction and omentoplasty after mediastinitis. Stoev H. Folia Med (Plovdiv) 2021;63(1):139-43. doi: 10.3897/folmed.63.e53706.
3. Deep wound infections (mediastinitis) after open heart surgery. H. Stoev, K. Dimitrov. MU - Plovdiv, Knowledge International Journal Vol. 34.4. Sep 2019, pp 911-913

Participation in scientific events:

1. Reconstruction of the sternum with titanium plate after severe osteomyelitis in a 59-year-old woman. Seventh National Congress of Thoracic, Cardiovascular and Vascular Surgery, Pravets, 2017
2. Deep wound infections in patients post open heart surgery with extracorporeal circulation. XVI National Congress of Surgery, Varna, Bulgaria, 2018.
3. Predictive role of troponin, C-reactive protein and natriuretic peptide in patients with coronary artery bypass grafting. Congress 15 years of pharmacy at the Medical University - Plovdiv, 2017
4. Dynamics of hs-CRP in patients after coronary artery bypass grafting with or without complications. - Poster. National Congress of Clinical Laboratory, 2017
5. Mediastinitis in patients post open heart surgery - prevention and predicting factors. Proceedings of the World Society of Cardiovascular and Thoracic Surgeons 29th Annual Congress, Sofia, Bulgaria, 2019, 14 (Suppl 1): O24