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Epidemiology and stratification of cardiovascular implantable electronic device (CIED) infections: results of a single-center retrospective study

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Abstract:	Purpose: Incidence of cardiovascular implantable electronic device (CIED) infections is increasing worldwide. However, no study was carried out in Hungary concerning CIED infections. Our goal was to estimate epidemiologic parameters and stratify CIED infections in a large adult population with permanent hardware. Methods: A single-center retrospective study was performed at the Hungarian Institute of Cardiology from 2011 through 2013. Cases were stratified whether infections occurred <3 months (early) or ≥3 months (late) after last implantation and by clinical manifestations (pocket infection, endocarditis, bacteremia, sepsis). Variables are expressed as means with standard deviations, numbers and percentages. Student's t-test, Mann-Whitney U-test, Fisher's exact test and Pearson's chi-squared test was used for data comparison, a 2-tailed p-value <0.05 indicated significance. Results: 62 episodes (40.3% early, 59.7% late) of 53 patients were identified, morbidity was 21±4.9 cases/year and 2.15 infections/100 device procedures. 13.2% of patients had infection recurrence. In-hospital mortality was 17.0%, risk factors were ≥3 device manipulations, sick sinus syndrome, CABG surgery, end-stage heart failure and sepsis. Pocket infections and bacteremias were frequent among early cases. Risk factors of early infection were device manipulation done within 3 months, postoperative pocket haematoma and permanent atrial fibrillation. Endocarditis and sepsis were common among late cases. Risk factors of late infection were device manipulation done beyond 3 months and previous CIED infection. Only late infections developed complications. Conclusions: According to clinical parameters, the heterogenous group of infections	

	can be divided into early and late cases which possibly carry different disease courses and outcomes.
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**Epidemiology and stratification of cardiovascular implantable
electronic device (CIED) infections: results of a single-center
retrospective study**

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ABSTRACT

Purpose: Incidence of cardiovascular implantable electronic device (CIED) infections is increasing worldwide. However, no study was carried out in Hungary concerning CIED infections. Our goal was to estimate epidemiologic parameters and stratify CIED infections in a large adult population with permanent hardware.

Methods: A single-center retrospective study was performed at the Hungarian Institute of Cardiology from 2011 through 2013. Cases were stratified whether infections occurred <3 months (early) or ≥ 3 months (late) after last implantation and by clinical manifestations (pocket infection, endocarditis, bacteremia, sepsis). Variables are expressed as means with standard deviations, numbers and percentages. Student's t-test, Mann-Whitney U-test, Fisher's exact test and Pearson's chi-squared test was used for data comparison, a 2-tailed p-value <0.05 indicated significance.

Results: 62 episodes (40.3% early, 59.7% late) of 53 patients were identified, morbidity was 21 ± 4.9 cases/year and 2.15 infections/100 device procedures. 13.2% of patients had infection recurrence. In-hospital mortality was 17.0%, risk factors were ≥ 3 device manipulations, sick sinus syndrome, CABG surgery, end-stage heart failure and sepsis. Pocket infections and bacteremias were frequent among early cases. Risk factors of early infection were device manipulation done within 3 months, postoperative pocket haematoma and permanent atrial fibrillation. Endocarditis and sepsis were common among late cases. Risk factors of late infection were device manipulation done beyond 3 months and previous CIED infection. Only late infections developed complications.

Conclusions: According to clinical parameters, the heterogeneous group of infections can be divided into early and late cases which possibly carry different disease courses and outcomes.

Keywords: cardiovascular implantable electronic device; CIED; CIED infection; epidemiology; risk factor

1. INTRODUCTION:

Cardiovascular implantable electronic devices (CIED) are non-valvular intracardial medical equipments gaining energy from an intra- or extracorporeal power supply. With newly formed and expanding evidence-based indications for implantation, pacemakers (PM), implantable cardioverter defibrillators (ICD) and cardiac resynchronization devices (CRT) are being implanted at increasing numbers worldwide [1,2]. However, usage of implantable hardware may be associated with serious complications, including life-threatening device infections. Incidence of CIED infections has been increasing over the past decades worldwide [1]. Estimated infection rate ranges from 0.8 to 5.7% among recipients, and the number of infections is growing out of proportion to rates of *de novo* device implantation [1,3,4].

CIED infections are typically caused by *Staphylococcus* species. Coagulase-negative *Staphylococci*, like *Staphylococcus epidermidis* account for approximately 40–45% of cases, 30% is caused by methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA). Infrequent pathogens are other Gram positive cocci, Gram negative bacilli, *Mycobacteria* and fungi [5–9]. Causative agents are either acquired from an endogenous source (skin, mucosa) or healthcare environment [1,7]. Device infections localised to the generator pocket are considered superficial infections. Deep infections are thought to spread from the pocket to transvenous segments of the device and can appear in several clinical forms (endocarditis, phlebitis, occult bacteremia, sepsis). Superficial and deep forms can rise synchronously in the same patient. Alternatively, device infections are considered primary if the device itself is the source of infection and secondary if the leads are seeded hematogenously from a distant focus due to bacteremia [10–12].

2. OBJECTIVES:

As of 2014, no study was carried out in Hungary concerning CIED related infections. Our goal was to estimate the epidemiologic parameters (morbidity, mortality and associated risk factors of infection), stratify and assess the clinical cases (onset, symptoms, complications and microbiology of infection) of CIED related infections among patients with different types of permanent CIEDs.

3. PATIENTS AND METHODS:

A single-center retrospective cohort study was performed. We analysed data of patients diagnosed and treated with CIED associated infections from January 1, 2011 through

December 31, 2013 at the 145-bed adult department of Gottsegen György Hungarian Institute of Cardiology (Budapest, Hungary), a tertiary care hospital with nationwide accessibility.

Patient selection and data:

Adult (≥ 18 years) patients were identified in hospital records by the following criteria: (1) diagnosis of CIED infection according to the International Classification of Diseases (ICD-10: T82.7) was assigned to the case at discharge; (2) implantation happened with a permanent PM, ICD or CRT; (3) diagnosis and treatment was completed at the Institute during the study period. Cases of secondary CIED infection were excluded from present study. General hospital data concerning CIED associated operations were also collected.

The following data were extracted from patient records: (1) basic identifying information; (2) previous and present diseases; (3) risk factors for infection (diabetes mellitus, malignancy, chronic renal insufficiency, long-term treatment with steroids or immunosuppressive therapy, oral anticoagulant use, postoperative pocket haematoma, operative device manipulation, artificial heart valve [7,8,10,13–19]); (4) prior implantations before disease; (6) date and hardware type of last implantation; (7) clinical form(s) of CIED infection; (8) first signs and symptoms at start of infection; (9) findings of microbiologic samples and echocardiography; (10) outcome and complications of infection. All patients underwent hardware removal and antibiotic therapy in accordance with the current guideline [1]. The institutional review board approved the study protocol.

Diagnostic methods:

Patients had 2 sets (1 hour delay) of aerobic and anaerobic blood samples (HC) taken through venipuncture at different sites within 12 hours upon admittance [20]. Lead tips and pocket samples containing excised tissue and pus were harvested in sterile containers during hardware removal. All samples were processed at the Microbiology Laboratory of Joined St. Stephan and St. Ladislaus Hospital–Clinic (Budapest, Hungary). Bacterial culturing and identification were performed according to standard microbiologic methods by using commercially available techniques. Causative infectious agent was confirmed if: (1) the organism was a known pathogen of CIED infection [1,21,22]; (2) identical resistance spectrums were held by the same species growing from different types of samples; (3) targeted antibiotic therapy was clinically successful. Microbiologic results considered to be originating from contamination were omitted. Every case was consulted with the department of infectology (GY.P.). Patients underwent transoesophageal echocardiography (TEE) within

48 hours upon admittance. Vegetation was defined as an oscillating intracardiac mass on device leads, cardiac valves or endocardial lining confirmed by TEE in >1 echocardiographic plane if deep CIED infection was presumable [9,10,23–25]. Vegetations were measured at different dimensions, the maximal length was used. Multiple vegetations were measured separately.

Definitions:

Device implantation and manipulation: A device procedure was defined as a *de novo* device implantation or a device manipulation. Device manipulation was defined as a surgical procedure during which a pre-existing generator pocket is opened percutaneously (generator exchange, lead adjustment or exchange, wound revision, haematoma evacuation, total hardware removal).

Early and late CIED infections: Infection cases between January 1, 2011 and December 31, 2013 were retrospectively stratified into an early (<3 months) or late ($\geq$ 3 months) group on the basis of the delay between the last device implantation and appearance of first clinical symptoms specifically related to CIED infection.

Clinical forms and complications of infection: Pocket infection was confirmed if clinical signs of local inflammation (tenderness, pain, erythema, swelling, warmth, fluctuance, wound dehiscence, generator site erosion [1,9,14]) were present along with negative TEE and HC culture findings (independently from results of pocket cultures). Endocarditis was confirmed if valvular or lead vegetations were detected by TEE or if modified Duke criteria of definite infective endocarditis were met [26–28]. Bacteremia was confirmed if positive HC samples provided causative agents but TEE findings were negative and endocarditis or other source of bacteremia could not be proven (bacteremias accompanying definite endocarditis were omitted from this group). Sepsis was defined if adult criteria of SIRS were met, systemic symptoms of infection were present and no septic focus could be confirmed other than the CIED [29,30]. If clinical forms appeared synchronously, the case was divided accordingly.

Device infection complication was defined as a previously undocumented abnormality or pathological progression found during hospital stay if its formation was specifically caused by CIED infection. Complications were diagnosed using echocardiography, 2-way chest radiography, chest and abdominal computed tomography and were grouped whether the lungs were affected (pulmonary) or spared (non-pulmonary).

Previous and recurrent CIED infections: Previous CIED infection was defined as a documented case in patient history, diagnosed and treated before the start of the study period.

Recurrent CIED infection was defined as the subsequent case after a prior one if both episodes appeared during the study period.

Statistical analysis:

Continuous variables are expressed as mean±standard deviation with minimum–maximum range, categorical variables are expressed as numbers and percentages relative to the given group. Variables of early vs. late cases are reported in this order. To compare early and late cases, we report odds ratios (OR) and their 95% confidence intervals (95% CI). Statistical analysis was performed using Student's unpaired t-test, Welch's t-test and Mann–Whitney U test for continuous variables, Fisher's exact test and Pearson's chi-squared test for categorical variables. A 2-tailed p-value <0.05 indicated statistical significance for all tests. Calculations were done using GraphPad Prism 5.0.

4. RESULTS:

1899/2882 (65.9%) of device procedures were *de novo* implantations (2011: 629, 2012: 635, 2013: 635), 983/2882 (34.1%) were device manipulations (2011: 330, 2012: 338, 2013: 315). 62 infective episodes (2011: 15, 2012: 23, 2013: 24) of 53 patients (75.5% men) were identified. 43/53 (81.1%) patients were ≥60 years of age (68.3±13.2 years, 25–89) with no difference between age of men and women (68.2±14.1 years, 25–89 vs. 67.8±9.8, 48–89; p>0.05). 23/53 (43.4%) patients had PMs, 19/53 (35.8%) had CRTs, 11/53 (20.8%) had ICDs at admittance. Overall incidence of CIED infections was 21±4.9 cases/year. Mean number of yearly infections was 2.15 per 100 device procedures (2011: 1.56, 2012: 2.36, 2013: 2.52). Among cases, risk factors and known diseases included device manipulation (71.0%), essential hypertension (69.4%), chronic heart failure (51.6%), oral anticoagulation (43.5%), multiple indwelling leads (37.1%), diabetes mellitus (33.9%), previous CIED infection (30.6%), permanent atrial fibrillation (22.6%), artificial heart valve (16.1%), malignoma (16.1%), chronic obstructive pulmonary disease (COPD, 14.5%), chronic renal insufficiency (9.7%) and postoperative pocket haematoma (8.1%).

CIED infections were early in 25/62 (40.3%), late in 37/62 (59.7%). Among early cases, incidence of pocket infections (84.0% vs. 51.4%; OR: 4.97; 95% CI: 1.42–17.34; p=0.01) and bacteremias (24.0% vs. 8.1%; OR: 3.58; 95% CI: 0.81–15.97; p>0.05) were higher. Endocarditis (20.0% vs. 45.9%; OR: 3.40; 95% CI: 1.05–11.0; p=0.03) and sepsis (4.0% vs. 16.2%; OR: 4.65; 95% CI: 0.52–41.24; p>0.05) were frequent among late infections. Synchronous superficial and deep infections were also identified (7/25, 28.0% vs.

3/37, 8.1%; OR: 4.41; 95% CI: 1.01–19.1; $p>0.05$) (Table 1). Clinical onset was delayed for years after implantation in late cases (1.5 ± 0.6 months, 2–12 vs. 63.8 ± 71.5 , 4–282; $p<0.0001$). Early pocket infections were likely to present with pocket erythema (61.9% vs. 10.5%; $p=0.001$) and pus (47.6% vs. 15.8%; $p=0.04$), signs of late pocket infection were pain (14.3% vs. 47.4%; $p=0.03$) and pocket ulceration (14.3% vs. 52.6%; $p=0.01$). Other signs of pocket infection ($p>0.05$): swelling (33.3% vs. 10.5%), pocket suffusion (14.3% vs. 0%), wound dehiscence (9.5% vs. 10.5%) and pocket fluctuation (9.5% vs. 10.5%). Trends in signs of deep infections were also noted ($p>0.05$). Endocarditis mostly presented with fever (100.0% vs. 88.2%), chills (40.0% vs. 29.4%), arthralgia (20.0% vs. 29.4%) and coughing (20.0% vs. 23.5%), some symptoms only appeared during late endocarditis: dyspnea (29.4%), chest pain (17.6%), confusion (17.6%), anuria (5.9%), anasarca (5.9%) and cachexia (5.9%). Bateriaemias produced fever (33.3% vs. 100%), chills (50.0% vs. 33.3%) and dyspnea (33.3% vs. 33.3%), coughing only presented during late cases (0% vs. 33.3%). First symptoms of sepsis were headache (100% vs. 66.6%) and hypotension (100% vs. 66.6%).

Risk factors of early infection include device manipulation done <3 months before onset of symptoms (64.0% vs. 8.1%; OR: 19.56; 95% CI: 4.65–82.29; $p<0.0001$), postoperative pocket haematoma (20.0% vs. 2.7%; OR: 9.0; 95% CI: 0.98–82.54; $p=0.03$) and permanent atrial fibrillation (40.0% vs. 10.8%; OR: 5.50; 95% CI: 1.48–20.40; $p=0.01$). Risk factors of late infection were device manipulation done ≥ 3 months before onset of infection (16.0% vs. 56.8%; OR: 16.33; 95% CI: 4.42–60.35; $p<0.0001$) and previous CIED infection (16.0% vs. 40.5%; OR: 3.58; 95% CI: 1.02–12.56; $p=0.04$). Observable trends ($p>0.05$) include essential hypertension (68.0% vs. 70.3%; OR: 1.11; 95% CI: 0.37–3.33), oral anticoagulation (56.0% vs. 35.1%; OR: 2.35; 95% CI: 0.83–6.64), chronic heart failure (52.0% vs. 51.4%; OR: 1.02; 95% CI: 0.37–2.83), multiple leads (36.0% vs. 37.8%; OR: 1.08; 95% CI: 0.38–3.10), diabetes mellitus (32.0% vs. 35.1%; OR: 1.15; 95% CI: 0.39–3.38), COPD (24.0% vs. 8.1%; OR: 3.57; 95% CI: 0.80–15.97), artificial heart valve (20% vs. 13.5%; OR: 1.60; 95% CI: 0.41–6.23), chronic renal insufficiency (8.0% vs. 10.8%; OR: 1.39; 95% CI: 0.24–8.26) and malignancy (8.0% vs. 21.6%; OR: 3.17; 95% CI: 0.61–16.41).

Overall in-hospital mortality specifically attributed to CIED infection was 9/53 (17.0%), average was 3.0 ± 3.5 patients/year (2011: 1, 2012: 7, 2013: 1). Device procedures were followed by death in 0.31%. All patients died despite successful hardware removal and adjuvant antibiotic therapy. Mortality was higher among late cases (12.0% vs. 16.2%; OR: 1.42; 95% CI: 0.32–6.29; $p>0.05$). Average time between hospital admittance and death was

32.7±10.7 (16–48) days, death occurred later among early cases (38.7±4.9 days, 33–42 vs. 29.7±11.4 days, 16–48; $p>0.05$). Compared to survived patients (44/53), people who died were younger (63.0±11.2 years, 41–76 vs. 69.3±15.2, 25–89; $p>0.05$) and frequently had endocarditis (66.7% vs. 36.4%; OR: 3.50; 95% CI: 0.77–15.94; $p>0.05$). Risk factors of in-hospital mortality were ≥ 3 device manipulations (33.3% vs. 6.8%; OR: 6.83; 95% CI: 1.11–41.99; $p=0.02$), coronary artery bypass graft (CABG) surgery (55.5% vs. 15.9%; OR: 6.61; 95% CI: 1.41–30.93; $p=0.02$), chronic heart failure (66.6% vs. 2.3%; OR: 86.0; 95% CI: 7.65–966.7; $p<0.0001$), sick sinus syndrome (44.4% vs. 6.8%; OR: 6.24; 95% CI: 1.24–31.26; $p=0.03$) and sepsis (44.4% vs. 6.8%; OR: 10.93; 95% CI: 1.87–63.67; $p=0.01$). Observable trends ($p>0.05$) include male gender (77.8% vs. 75.0%, OR: 1.17; 95% CI: 0.21–6.47), implanted CRT (55.5% vs. 31.8%; OR: 2.68; 95% CI: 0.62–11.5), diabetes mellitus (55.5% vs. 36.4%; OR: 2.18; 95% CI: 0.51–9.34), complicated (33.3% vs. 25.0%; OR: 1.50; 95% CI: 0.32–7.03) and recurrent CIED infection (22.2% vs. 11.4%; OR: 2.23; 95% CI: 0.36–13.85).

Considering pocket samples, rate of culture-positivity was higher in early pocket infection cases (61.9% vs. 52.6%; $p>0.05$). In contrast, HC culture-positivity was higher among late deep infections (91.7% vs. 96.2%; $p>0.05$), lead tip cultures were of low positivity rate (16.7% vs. 7.7%; $p>0.05$). Among synchronous superficial and deep infections, same species of bacteria were isolated from blood and pocket cultures in low numbers (42.9% vs. 33.3%; $p>0.05$). Of all early (24/25, 96.0%) and late (35/37, 94.6%) culture-positive cases, dominant pathogens were ($p>0.05$) *S. aureus* (70.8% vs. 57.1%), *S. epidermidis* (8.3% vs. 22.9%), *Enterococcus faecalis* (4.2% vs. 5.7%) and *Escherichia coli* (4.2% vs. 2.9%), while minor pathogens were *Acinetobacter baumannii* (4.2% vs. 0%), *Enterobacter cloacae* (4.2% vs. 0%), *Serratia marcescens* (4.2% vs. 0%), *Pseudomonas aeruginosa* (0% vs. 8.6%) and *Streptococcus viridans* (0% vs. 2.9%). 5/59 (8.5%) culture-positive cases were polymicrobial. Trends ($p>0.05$) in the occurrence of different pathogens were established: *S. aureus* was common in early pocket infections (69.2% vs. 40.0%), endocarditis (75% vs. 62.5%), bacteremia (44.4% vs. 33.3%) and sepsis (100.0% vs. 71.4%), *S. epidermidis* was prevalent in late pocket infections (15.4% vs. 30.0%), endocarditis (0.0% vs. 18.8%), bacteremia (11.1% vs. 33.3%) and sepsis (0.0% vs. 14.3%), Gram negatives were dominant in early endocarditis (25% vs. 6.3%) and bacteremias (44.4% vs. 0%), also in late pocket infections (7.7% vs. 30.0%) and sepsis (0% vs. 14.3%). Synchronous infections were mainly caused by *S. aureus* (5/10, 50.0%). Also, *S. aureus* was the dominant microbe among cases of in-hospital death (6/9, 66.7%).

9/62 (14.5%) infections of 7/53 (13.2%) patients were identified as recurrent cases. Late recurrences were more frequent (6.5% vs. 8.1%; OR: 2.06; 95% CI: 0.49–8.59; $p>0.05$); 4/62 (6.5%) were early and 3/62 (4.8%) were late pocket infections, 1/62 (1.6%) was late endocarditis, 1/62 (1.6%) was late sepsis. All recurrent pocket infections had a previous case of pocket disease, endocarditis had a prior bacteremia, sepsis was preceded by endocarditis. Average delay between the clinical end of last infection and appearance of first symptoms associated with recurrence was 11.2 ± 14.2 (1–44) months, late recurrent infections appeared nearly 2 years after the first episode (1.8 ± 0.8 months, 1–3 vs. 23.0 ± 14.2 , 13–44; $p=0.05$). *S. aureus* was isolated from 3/62 (4.8%), *S. epidermidis* was found in 2/62 (3.2%), negative cultures were obtained in 4/62 (6.5%). All cultured pathogens of recurrent infections corresponded to the causative agent of prior episodes. Compared to people without recurrences (46/53), patients were younger (66.9 ± 14.2 years, 37–79 vs. 68.5 ± 13.2 , 25–89; $p>0.05$). Risk factor of recurrence was any electrode fragment remaining after hardware removal performed during prior infections (66.7% vs. 22.6%; OR: 6.83; 95% CI: 1.48–31.50; $p=0.01$). Trends ($p>0.05$) were male gender (77.8% vs. 62.3%; OR: 2.12; 95% CI: 0.40–11.24), device manipulation in patient history (77.8% vs. 69.8%; OR: 1.51; 95% CI: 0.28–8.10) and diabetes mellitus (55.6% vs. 30.2%; OR: 2.89; 95% CI: 0.69–12.20). In-hospital mortality was 2/7 (28.6%) among patients with recurrent infections.

Among 14/53 (26.4%) patients, 13/20 (65.0%) non-pulmonary and 7/20 (35.0%) pulmonary complications were identified. 7/53 (13.2%) people developed non-pulmonary, 6/53 (11.3%) had simultaneous pulmonary and non-pulmonary, 1/53 (1.9%) only had pulmonary complications. In-hospital mortality was 3/14 (21.4%). Complications were only observed in the late group (0% vs. 37.8%; OR: 31.47; 95% CI: 1.78–557.80; $p=0.0003$). 6/7 (85.7%) pulmonary complications corresponded to chronic multiple seeding, 1/7 (14.3%) was acute massive pulmonary embolism. Endocarditis was found in 7/7 (100%), synchronous sepsis developed in 4/7 (57.1%). Signs of pulmonary involvement were typical compared to symptoms of patients without complication (39/53): fever (85.7% vs. 51.3%; $p>0.05$), dyspnea (57.1% vs. 12.8%; $p=0.01$), coughing (42.9% vs. 12.8%; $p>0.05$), chest pain (28.6% vs. 2.6%; $p=0.04$) and haemoptysis (28.6% vs. 0%; $p=0.01$). Non-pulmonary complications were 7/13 (53.8%) newly formed or deteriorating tricuspid valve insufficiencies, 1/13 (7.7%) paravalvular leak, 1/13 (7.7%) mediastinitis from a pocket–pleura fistula, 1/13 (7.7%) pleural empyema, 1/13 (7.7%) splenic abscess, 1/13 (7.7%) septic spondylodiscitis with psoas muscle abscess and 1/13 (7.7%) phlebothrombosis of the right subclavian vein. 12/13 (92.3%) non-

pulmonary complications were associated with endocarditis, 1/13 (7.7%) with pocket infection. Non-pulmonary complications produced diverse signs according to the main affected organ(s).

5/5 (100%) early and 14/17 (82.4%) late endocarditis cases had detectable vegetations using TEE ($p>0.05$). Altogether 6/24 (25.0%) early and 18/24 (75.0%) late vegetations were identified. Rate of cases with multiple vegetations was similar between groups (20.0% vs. 21.4%; $p>0.05$). Average vegetation size was greater in the late group (8.2 ± 5.3 mm, 2–17 vs. 19.8 ± 17.4 mm, 7–80; $p=0.02$). Most frequent location of vegetations ($p>0.05$) was the right atrium (33.3% vs. 50.0%), followed by the right ventricle (33.3% vs. 22.2%), mitral valve (16.7% vs. 11.1%), tricuspid valve (0% vs. 11.1%), left ventricle (0% vs. 5.6%) and aortic valve (16.7% vs. 0%). Early-case vegetations did not give septic embolism (0%), 10/18 (55.6%) late vegetations seeded towards the pulmonary (50%) or systemic (5.6%) circulation (0% vs. 55.6%; $p=0.02$). According to positive HC samples, 5/5 (100%) early cases were caused by MSSA, late infection was caused by MSSA in 6/14 (42.9%), MRSA and also *E. faecalis* in 2/14 (14.3%) each, and *S. epidermidis* in 1/14 (7.1%).

5. DISCUSSION:

The present single-center retrospective study of CIED related infections is the first one carried out in Hungary. We estimated epidemiologic parameters concerning CIED related infections and stratified cases of infections into groups before examining their features accordingly to develop a better understanding of disease characteristics for clinicians.

Average incidence of CIED infection was 21 ± 4.9 cases/year among patients, rising incidence could be proven. The rate of disease is similar to the results reported by other authors [1,6,31]. Most affected patients were elderly men. Known risk factors of CIED infection found in literature were well reflected in our study population. 13.2% of patients had infection recurrence, mostly pocket infections. In-hospital mortality of CIED infections was similar to the number found by others [32]. Patients who died usually were younger males implanted with CRTs and developing endocarditis. Most fatal cases were late onset and caused by *S. aureus*. This finding is supported by a study in which increased mortality was attributed to deep *S. aureus* CIED infections [31]. We identified new risk factors of in-hospital mortality: ≥ 3 device manipulations, sick sinus syndrome, CABG surgery in patient history and sepsis. Chronic heart failure was described earlier as a predictor of increased

mortality [33]. We found that mortality was higher among patients with complications and 3.8% of patients died during episodes of recurrent infection.

We showed that the heterogenous group of CIED infections could be stratified into early and late subgroups. Most early diseases appear shortly after implantation as pocket infections or bacteremias. Significant risk factors of infection were postoperative pocket haematoma, permanent atrial fibrillation and device manipulation done within 3 months before the onset of infection. Majority of late cases manifested years after implantation as endocarditis or sepsis. Significant risk factors for late infection were device manipulation done beyond 3 months before onset and previous CIED infection. Device manipulation was noted as a risk factor by other groups [10,16,18], although correlation of the time delay between manipulation and onset of infection was not emphasized. We showed that timing of previous device manipulations is crucial in the development of both early and late infections.

The probable pathogenesis of early infections is perioperative wound contamination with virulent Gram positive bacteria. This idea is supported by that *S. aureus* is the main pathogen isolated from early microbiologic samples, as well that prevalent clinical forms were often locally destructive pocket infections and occult bacteremias. Similar results were shown in the literature [34]. The main pathogen of late infections was *S. epidermidis*, a member of the normal skin flora. Considering this, we assume that postoperative endogenous contamination with less virulent Staphylococcal strains and forming of biofilm on the surface of the CIED may be principal steps in the patogenesis of late disease. Bacteria in biofilms could persist for months, even years [31].

We showed that symptoms were specific in cases of pocket infection: early cases showed pocket erythaema and pus at greater rates, late ones rather developed pain and pocket ulceration. Occurence of pocket dehiscence and fluctuation was independent of onset. Deep infections appeared with sympmtoms of systemic infection as described earlier by others [10,11,35]. Complications do not appear essentially during disease course but may aggravate or modify outcome in a negative manner. 26.4% of patients had complications. Only late infections developed complications, the dominant clinical form was endocarditis. Pulmonary complications had characteristic symptoms (fever with coughing, haemoptysis, dyspnea, chest pain) which should always be suspicious for CIED infection in patients with indwelling hardware.

Possible limitations to this study could be report bias of cases and the relatively low disease count despite the large cohort of included patients which may impact statistical significance. However, we believe that tendencies showed in present study apply generally and a multi-center prospective study carried out in Hungary could provide further data on possible clinical stratification and disease outcomes.

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6. COMPLIANCE WITH ETHICAL STANDARDS:

The work described has not been published before, it is not under consideration for publication anywhere else and its publication has been approved by all co-authors, as well as by the responsible authorities at the institute where the work has been carried out.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: For this type of study formal consent is not required. The institutional review board approved the study protocol. This article does not contain any studies with animals performed by any of the authors.

Informed consent: The manuscript does not contain clinical studies or patient data.

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8. TABLES

Clinical forms of CIED infection	Early cases (n=25)		Late cases (n=37)	
	Number	Percent (%)	Number	Percent (%)
Pocket infection alone	14	56.0	16	43.2
Pocket infection with bacteremia	4	16.0	0	0.0
Pocket infection with endocarditis	3	12.0	1	2.7
Pocket infection with sepsis	0	0.0	1	2.7
Pocket infection with endocarditis and sepsis	0	0.0	1	2.7
Bacteremia alone	2	8.0	3	8.1
Endocarditis alone	1	4.0	11	29.7
Endocarditis with sepsis	1	4.0	4	10.8

Table 1. Synchronous appearances of clinical forms in cases of early and late CIED infections

Clinical forms of CIED infection	Early cases (n=25)		Late cases (n=37)	
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Pocket infection alone	14	56.0	16	43.2
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