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Etiology, Clinical Manifestations and Microbiological Profile of Cardiac Device Infections

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Abstract

Introduction: Cardiovascular implantable electronic device infections (CIEDIs) cause a lot of serious clinical problems among which lead dependent infective endocarditis (LDIE) is considered to be the worst.

Background: The background of the study was to analyze the parameters of clinical manifestations, determine the etiology and microbiological profile of the infections as well as evaluate the role of echocardiography in diagnosing LDIE.

Methods: Retrospective examinations were carried out in Reference Clinical Cardiology Centre in Lublin, Poland. The study group comprised 767 patients who between 2009 and 2014 underwent transvenous lead extraction (TLE) for infective and non-infective reasons.

Results: The study group comprised 382 patients with infective complications and 385 without infection. CIEDI group included 30.1% LDIE patients, 38.48% pocket infection patients (PI) and 31.41% mixed LDIE and PI patients. Fever was most frequently reported in LDIE patients. Significantly more LDIE patients were found to suffer from concomitant infections. LDIE group comprised significantly more patients with hs-CRP>50 mg/dL. Analysis of microbiological data showed that the most common cause of the infective complications were *Staphylococcus epidermis* and *Staphylococcus aureus*. Echocardiography examination revealed the presence of vegetation in 78.26% of LDIE patients in TEE and in 63.48% in TTE.

Conclusions: Fever and concomitant infections predominated in the clinical picture of LDIE. Hs-CRP value proved to be essential for diagnostic procedures. TEE examination proved to be more effective in revealing vegetation than TTE. The most common cause of infective complications was *S. epidermidis* and *S. aureus* which points out to the endogenic source of infections.

Keywords: Cardiovascular electronic device infections; Lead dependent infective endocarditis; Pocket infection; Biofilm; Vegetation

Introduction

Infections developing in patients with cardiac implantable electronic devices including permanent pacemakers (PMs), implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy devices (CRT) are causing considerable clinical problems. Lead dependent infective endocarditis (LDIE) is considered the most serious complication. LDIE symptoms are similar to clinical features of respiratory track infective disease and so some diagnostic difficulties may arise. Cardiovascular implantable electronic device infections as reported by the world registries range between 0.13% and 19.9% for PMs and 0.8% for ICDs and roughly 10% to 25% of these patients develop LDIE [1-14].

Background

The background of the study was to analyse the parameters of clinical features, etiology and microbiological profile of the infections. We also aimed at evaluating the role of echocardiography in detecting LDIE in 767 implantable electronic device patients undergoing transvenous lead extraction (TLE).

Material and Methods

Retrospective examination was conducted at clinical cardiology centre in Lublin, a referral centre in Poland, which deals with implantable electronic device infections. The study group comprised 767 infective and non-infective patients who between 2009 and 2014 underwent transcutaneous extraction of PMs/ICDs/CRT. The group consisted of 382 patients with infections (49.8%) and 385 without infections (50.2%). The latter were referred for TLE either because some elements of the device were damaged; malfunctioning or technologically more advanced device was installed. LDIE was diagnosed on the basis of modified Duke's criteria when two major, at least one major and three minor or five minor criteria were met. In case of site infection symptoms including erythema, swelling, increased warmth and abscess, and when no additional criteria for LDIE were found, pocket infection (PI) was diagnosed. Patients with infections were evaluated in terms of parameters of clinical manifestations, laboratory test results, microbiological profiles and echocardiography results (the presence and size of vegetation and its

most frequent localization in cardiovascular system). Taking all this into consideration we were able to identify major factors leading to proper diagnosis.

Statistical analysis

Statistical analysis was performed with "Statistics" software. Qualitative variables were compared by means of Chi-square test, whereas quantitative parameters were calculated with mean value standard deviation (± SD) and median (Me). In case of normal distribution of variables and homogenous P-value Student's T-test was used to evaluate the differences between particular groups. The variables were compared using the mean value and standard deviation whereas quantitative parameters were calculated with mean value standard deviation (± SD). However, when the distribution was different from the normal the differences between groups were calculated with U-Mann-Whitney test for two independent groups. The variables were compared using median (Me). Shapiro-Wilk test was used to check the conformity of the evaluated groups with the standard distribution. 5% error was accepted and two-tailed P-value<0.05 was considered statistically significant.

Results

The study group comprised 382 patients with infective complications (49.8%) and 385 without infection (50.2%). Among patients with infection there were 115 LDIE (30.1%), 147 PI (38.48%) and 120 LDIE+PI patients (31.41%). Fever was reported most often in LDIE patients (36.52% *vs.* 5.44%; p=0.0001 for LDIE *vs.* PI and 36.52% *vs.* 16.67%; p=0.0001 for LDIE *vs.* LDIE+PI). LDIE patients had mean body temperature higher than PI (37.4°C *vs.* 36.8°C) and LDIE+PI (37.4°C *vs.* 37°C). Most PI patients had either proper or slightly elevated temperature. LDIE group comprised significantly more patients with concomitant infections of urinary, respiratory, dermal and neurological systems than PI group (22.61% *vs.* 10.2%; p=0.006, whereas no significant differences were noted between LDIE and LDIE +PI patients (22.61% *vs.* 18.55%; p=0.41). Analysis of laboratory parameters showed that leukocytosis (WBC>10.5 × 10^3/μl) was much more common in LDIE patients than PI patients (29.57% *vs.* 12.93%; p=0.002). Median for WBC value in LDIE patients was within standard; however, it was higher than in PI patients (8.57 × 10^3/μl *vs.* 7.5 × 10^3/μl) and in LDIE+PI patients (8.57 × 10^3/μl *vs.* 8.21 × 10^3/μl). It was also noted that significantly more LDIE patients than PI patients had WBC between 10 and 20 × 10^3/μl and most PI patients had WBC between 5 and 10 × 10^3/μl. The above differences were statistically significant (p=0.0006). The highest concentration of CRP was found in LDIE patients. There were significantly more LDIE patients with CRP>50 mg/dl than in the other two groups (p=0.0001 for LDIE *vs.* PI and p=0.0002 for LDIE *vs.* LDIE+PI). CRP mean value for LDIE was higher than in the other two groups (33.2 mg/dl *vs.* 6.7 mg/dl for LDIE *vs.* PI and 33.2 mg/dl *vs.* 11.73 mg/dl for LDIE *vs.* LDIE+PI). Among LDIE patients higher than normal procalcitonin concentration (PCT) was reported most often (p=0.0001 for LDIE *vs.* PI and p=0.0001 for LDIE *vs.* LDIE+PI). Mean PCT value in this group was higher than in the other two, but it was still within standard (0.14 ng/ml *vs* 0.075 ng/ml for LDIE *vs.* LDIE+PI). LDIE patients were found to have the lowest Hb concentration. The group comprised significantly more patients with Hb below 10 mg/dl compared to PI patients (p=0.0001) and more patients with Hb below 9 mg/dl compared to LDIE+PI patients (p=0.0002). Hb mean value was lower in LDIE patients compared to PI (12.1 mg/dl *vs* 13.5 ± 1.78 mg/dl) and slightly lower than in LDIE+PI (11.86 ± 2.2 mg/dl *vs* 12.68 ± 1.87 mg/dl). The differences were statistically significant (Table 1).

Clinical and laboratory parameters		LDIE (n=115)	PI (n=147)	LDIE+PI (n=120)
Fever (temp>38 °C)%		36.52	5.44	16.67
Concomitant infections of other systems %		22.61	10.2	18.33
Leukocytosis (>10.5 x 10^3/μl) %		29.57	12.93	20
WBC (x 10^3/μl)	$\bar{x}$ ± SD	9.65 ± 4.83	7.99 ± 2.56	8.57 ± 3.22
	Me	8.57	7.5	8.21
CRP ≥ 5.0 mg/dl%	$\bar{x}$ ± SD	83.48%	57.14	70.83
CRP (mg/dl)		55.68	15.74	30.64
	Me	33.2	6.7	11.73
PCT ≥ 0.5 ng/ml %		15.91	2.94	9.09
PCT (ng/ml)	Mean value ± SD	3.06	0.13	0.59
	Me	0.14	0.075	0.03
Hb (K: Hb<12 g/dl; M: Hb<14 g/dl)%		68.7	52.38	58.33
Hb (g/dl)	$\bar{x}$ ± SD	11.86 ± 2.2	13.24 ± 1.78	12.68 ± 1.87
	Me	12.1	13.5	12.7

Table 1. Clinical and laboratory parameters in patients with CDI who underwent TLE between 2009 and 2014.

The present study showed that the most common cause of infective complications were CoNS bacteria out of which *S. epidermidis* was a prevailing one. The second most frequently isolated pathogen was *S. aureus*. The other pathogens occurred rarely were: *S. hemolyticus, Enterobacter cloacae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Streptococcus mitis*.

Positive blood culture results were obtained in 15.16% of patients with infections. The most commonly isolated pathogens were CoNS (40.43%) and *S. aureus* (29.79%, MRSA-8.51%, MSSA-21.28%). CoNS contained 20.36% MRCNS and 20.1% MSCNS. *S. epidermidis* proved to be most frequent pathogen, which was isolated in 21.28% cases (MRSE–10.64%, MSSE-10.64%). Other CoNS bacteria were isolated in 19.15% cases and included *S. haemolyticus, S. capitis, S. hominis and S. saprophyticus* (Figure 1).

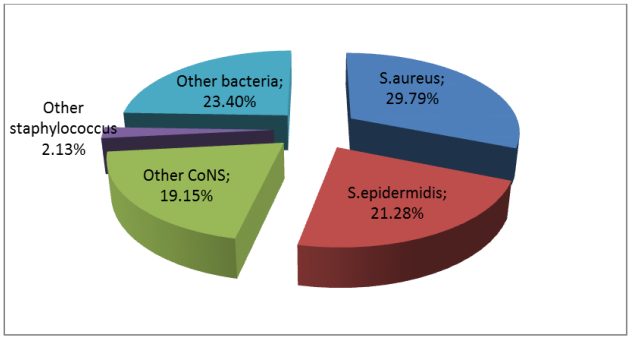

Figure 1: Distribution of microorganisms in blood cultures of CDI patients.

Positive lead cultures were detected in 55.08% cases. The most common pathogens were CoNS (69.27%) and *S. aureus* (19.27%, MRSA-3.65%, MSSA-15.63%). CoNS comprised 38.86% MRCNS and 38.29% MSCNS. Prevailing *S. epidermidis* was detected in 52.08% cases (MRSE-29.17%, MSSE-22.92%). Other CoNS pathogens were isolated in 17.19% cases and included *S. haemolyticus, S. capitis, S. simulans, S. cohnii, S. hominis, S. saprophyticus, S. warneri and S. xylosus*. In 11.46% of cases less common bacteria were detected. They included *E. coli, E. faecalis, E. cloacae, E. aerogenes, A. baumanii, K. pneumonia, K. Kristinae, P. aeruginosa, P. mirabilis, Str. mitis, Str. agalactiae* (Figure 2).

Positive cultures of pocket were revealed in 59.41% infective patients. Most frequently isolated pathogens were CoNS (63.16%) and *S. aureus* (21.05%, MRSA-6.02%, MSSA-15.04%). CoNS comprised 37.7% MRCNS and 31.15% MSCNS. Dominating *S. epidermidis* was isolated in 48.87% of cases (MRSE-26.32%, MSSE-22.56%) other CoNS pathogens were detected in 14.29% of cases and included *S. haemolyticus, S. hominids, S. saprophyticus and S. schleiferi* (0.75%). In 13.53% of cases less common bacteria were isolated *E. coli, E. faecalis, E. cloacae, C. freundii, A. baumanii, P. aeruginosa, P. mirabilis*. Fungi were found in 1.5% of cases and included *Candida albicans* and *Aspergillus fumigatus*.

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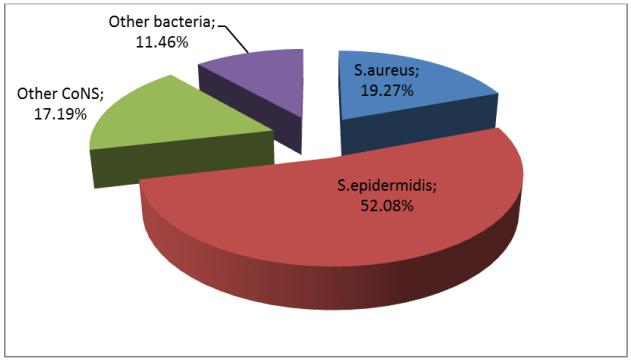

Figure 2: Distribution of microorganisms in explanted lead cultures in patients with CDIs.

Blood culture results showed that *S. epidermidis* was isolated more often in infections developing after 12 months of device implantation and *S. aureus* within 12 months. Culture results in leads represented similar values but the differences were not statistically significant. Pocket cultures results suggested that *S. epidermidis* and *S. aureus* alike were responsible for developing site infection within or after 12 months (Table 2). It was also observed that CoNS occurred more frequently than *S. aureus* in patients with inactive leads (36.84% *vs.* 7.14%), but the differences were not statistically significant. Additionally, CoNS were more frequent than S.aureus in patients with at least 3 leads (36.84% *vs* 7.14%), but the differences were not statistically significant.

Positive culture (+)	*S. epidermidis*		*S. aureus*	
	≤ 12 month	>12 month	≤ 12 month	>12 month
Blood culture %	17.65	23.33	47.06	20
Lead culture %	48.57	54.1	25.71	15.57
Pocket culture %	50	48.05	23.21	19.48

Table 2: Comparison of the number of *S. epidermidis* and *S. aureus* related infections depending on the time from implantation to the onset of symptoms.

Echocardiography examination revealed the presence of vegetation in 78.26% of patients with isolated LDIE and in 50.83% of patients with isolated LDIE+PI. Our study confirmed that TEE (transesophageal echocardiography) is more effective in detecting vegetation in both groups than TTE (transthoracic echocardiography). More extended vegetation were more often detected in patients with isolated LDIE. Vegetation ranging up to 1 cm was most common (25.22% *vs* 30% for LDIE *vs.* LDIE+PI). Next came vegetation ranging between 1 and 2 cm (45.65% *vs* 17.5%, respectively). Extended vegetation over 2 cm was more frequent in LDIE (17.39% *vs* 5% for

LDIE *vs.* LDIE+IM). Right atrium appeared to be most common location for vegetation in both groups (53.91% *vs.* 40%). The second most common was superior vena caval orifice (15.65% *vs.* 5.83%), then came right ventricle (10.43% *vs.* 11.67%), tricuspid valve (12.17% *vs.* 2.5%) and some single locations in left atrium and left ventricle (2.6% *vs.* 0%) (Table 3).

		LDIE	LDIE+IM
Vegetation %		(+) 78.26	(+) 50.83
		(-) 21.74	(-) 49.17
Vegetation revealed in TTE %		63.48	35.83
Vegetation revealed in TEE %		78.26	50.83
Vegetation %	Small (<1 cm)	25.22	30
	Medium (1-2 cm)	35.65	17.5
	Large (>2 cm)	17.39	5
Location %	Right atrium	53.91	40
	Superior vena cava orifice	15.65	5.83
	Right ventricle	10.43	11.67
	Tricuspid valve	12.17	2.5
	Mitral valve	2.6	0

Table 3: Echocardiography results (presence, size and location of vegetation in the heart) in patients undergoing TLE between 2009 and 2014.

Discussion

Clinical manifestations of infections, especially LDIE in patients with implanted cardiac devices, are nonspecific and as such, often detected too late. It necessitates more thorough examination of a variety of clinical and laboratory parameters which will help identity and distinguish this condition from other infections of similar clinical symptoms.

Analysis of clinical and laboratory data suggested that body temperature level and infective parameters in patients referred for TLE were significantly elevated compared to control group. Fever and accompanying infections of other organs could be observed mostly in LDIE patients. This group of patients represented elevated infective parameters of WBC, CRP, PCT and the lowest Hb concentration. CRP appeared to be most sensitive indicator for LDIE. CRP concentration was elevated in 83.48% of LDIE patients, with median of 33.2 mg/dl. LDIE group comprised 29.57% of patients with leukocytosis and 15.91% of patients with elevated PCT concentration. Median value was about the norm, and was 8.57×10^3/ul for WBC and 0.14 ng/ml for PCT. The lowest infective values and temperature levels were recorded in PI patients. Golzio et al. [15] compared laboratory parameters in patients with suspected LDIE and PI. Statistically significant higher OB, CRP and WBC inflammation parameters were noted in LDIE than PI patients. Ipeak at al. [16] examined a group of 34 patients with infection 70% of whom were PI patients. The whole group was reported with elevated levels of CRP and OB but low WBC values in the whole group. Polewczyk [17], reported elevated CRP levels and suggested they may be regarded as predictive values for LDIE. Additionally, WBC concentration proved not to be elevated in the whole LDIE group. Sohail et al. [14] examined 189 patients with PMs and ICDs, 44 of whom suffered implant related infection. Most patients with infection were reported to have elevated OB and WBC parameters. Infective complications appear to be in strict correlation with higher inflammatory parameters, mostly CRP and OB. WBC values are variated, which suggests that it is not an indicator sensitive enough to identify these diseases and its variability in CIED infective complications has not been fully accounted for. The present study showed that CRP appeared to be the most sensitive indicator of infection especially LDIE. Although high WBC concentrations were stated in considerably more LDIE patients than PI or LDIE+PI patients, median was about the norm.

One of the most common diagnostic methods for LDIE is TEE and TTE. TTE method has its weak points owing to problems with visualization which are caused by reverbations i.e. multiple reflections of ultrasound waves from endocardiac leads. Additionally, vegetation is often located in right atrium, tricuspid valve or superior vena caval orifice-the sites which are inaccessible for TTE [18,19]. TTE sensitivity is often not high enough to detect LDIE (23 to 26% efficacies). TEE offers better visualization of the above mentioned sites and consequently the detection of vegetation is higher (59 to 63%), which results in more effective diagnosis compared to TTE [18,20]. Thus, TEE is commonly chosen to diagnose LDIE and to monitor the course of treatment after endocardiac leads removal [13,15,21-23]. Our study confirmed the advantage of TEE over TTE in identifying vegetation. Among LDIE patients, vegetations were found in 78.26% and LDIE+PI in 50.83% of cases. In LDIE group vegetation was detected in 63.48% of patients with TTE and in 78.26% with TEE examination. In LDIE +PI group the proportions were more or less the same, for TTE-35.83% and for TEE-50.83%. In both groups vegetations were mostly found in right atrium (53.91% *vs* 40%), but in a lot of LDIE patients vegetations were located in the superior vena caval orifice (15.65%) and in the right ventricle (10.43%). There were patients with several concomitant vegetations developed in different parts of the heart. Golzio et al. [15] examined 293 patients including 136 patients with CDI. TEE examination revealed vegetation in 62.2% patients with LDIE and 21.9% with PI. This gave rise to the assumption than TEE examination should be performed when LDIE is suspected and accompanied by pocket infection but no systemic symptoms or major abnormalities in laboratory parameters are reported. Polewczyk [30] presented similar analysis. She estimated the efficacy of TTE and TEE examinations in detecting vegetations (30.3% and 60.9%, respectively). Additionally, right atrium and superior vena caval orifice proved to be the most common vegetation site (81.8% and 27%, respectively).

Our study also aimed at determining microbiological profile of the infections and their sources. Analysis of the group with infections revealed 15.6% of cases with positive blood culture results out of which 27% were LDIE and 13.33% were LDIE+PI patients. In PI patients, positive blood cultures results were non-diagnostic (one out of minimum two cultures was positive) and affected by impurities found on patients' skin. CoNS especially S.epidermidis was the pathogen most often found in blood cultures. The second most frequent was *S. aureus*. In patients with isolated LDIE there were 33.33% CoNS out of which 18.52% were *S. epidermidis* (MRSE-11.11%) and 29.93% *S. aureus* (MRSA- 7.41%). In LDIE+PI patients there were 28.57% CoNS out of which 7.14% were *S. epidermidis* and the remaining 21.43% constituted other types of *staphylococcus* including *S. haemolyticus*, *S. capitis* and *S. hominis, S. aureus* was isolated in 50% of cases

(MRSA-14.29%). Other bacteria were scarce in LDIE patients-33.33% and LDIE+PI14.29% and they included *Escherichia coli, Enterococcus faecalis, Klebsiella pneumoniae, Ochrobacterium antrophi* and *Streptococcus pneumoniae*. Two LDIE patients had *Candida albicans* and *Candida glabrata* fungi. Negative culture results were obtained in 73% LDIE and 86.67% LDIE+PI patients as a consequence of antibiotic treatment that the patients had received before they were admitted to hospital. Studies carried out worldwide report that the most often isolated pathogens taken from blood cultures were CoNS and *S. aureus*. Recommendation concerning diagnostics, prevention and treatment of implantable cardiac device infection patients are based on the results obtained from 18 centres located in North America, Europe and Australia. It has been concluded that *staphylococcus* accounted for 68 to 93% of infective complications. The dominating two were *S. epidermidis* (10-68%) and *S. aureus* (24-59%). Additionally, in studies carried out on a group of 100 patients, methicillin resistant CoNS was found in 33% of patients in Italy and 50% in USA. In groups comprising over 100 patients, methicillin resistant CoNS was found in 12.5% of patients in Australia, 29% in France and 54-80% in Great Britain. *S. aureus* associated infections resistant to methicillin were reported in 2.6% cases in Germany and up to 55% in USA. In 2013 the incidence of *S. aureus* related infections was 18.8/100 thousand cases out of which 9% were strains resistant to methicillin. Gram negative rods were isolated in 1-17% cases, Enterococcus in 5-6% cases and *Streptococcus* in 4-6% cases. Fungi were found in 2% of cases. One of the studies presents reports from 12 countries where infections were diagnosed on the basis of clinical manifestations and points out that in 12-49% cases negative blood culture results were obtained [17]. Other reports present similar results [2,5,14,24-28].

In our studies we have observed that patients with *S. aureus* dominating in blood and lead end cultures developed infection within 12 months of implantation whereas *S. epidermidis* took over 12 months to develop. It was also stated that in pocket infection cultures, *S. aureus* occurred as often as *S. epidermidis*, independent of the time between implantation and infection onset. However, some reports confirm that *S. aureus* takes shorter time to develop after implantation than *S. epidermidis* [29,30]. It has been observed that 45% patients with *S. aureus* in their blood cultures developed infection in a year. After a year, *S. aureus* related infections were scarcely reported [31]. Taking this into account, it has been recommended that the moment *S. aureus* is detected the whole PM/ICD/CRT device be removed instantly, irrespective of clinical manifestations or vegetations found in echocardiographic examination.

Another problem is connected with the results received from cultures from extracted lead ends. Currently researchers are of different opinions some claim that positive blood culture is a major Duke criterion for LDIE, others do not consider them to be relevant diagnostic signs as there is a possibility that the lead might have been contaminated with bacteria from infected pocket during extraction [32]. According to different sources, positive cultures of lead ends in case of pocket infection are found in 79.3%- 87.5% [14,18]. It has been suggested that positive lead cultures might indicate that the infection is spreading to endocardium and consequently, patients with PI should be referred for TLE just after it was diagnosed [12,33]. Mayo Clinic does not recognize lead culture results as a diagnostic criterion for LDIE. They claim that positive lead cultures may be decisive in diagnosing LDIE only in case of lack of pocket infection when the device was extracted far from the pocket or in the case of cardio-surgical device extraction [13,14,18]. In our study, we obtained 43.62% of positive culture results of extracted leads in patients with LDIE, 77.16% in patients with LDIE+PI and 54.76% in patients with PI. This is quite a big amount, taking into account the fact that lead extraction was performed with particular attention so as to prevent lead contamination with skin physiological flora or with pocket bacteria. The above observations suggest that lead cultures should be taken into consideration while diagnosing LDIE but the possibility of lead contamination during TLE cannot be excluded. Analysis of the microbiological studies of the lead showed that CoNS (69.27%) and *S. aureus* (19.27%) were most often isolated pathogens. Other microorganism was found in 11.76% cases. Among them were *E. coli*, *E. faecalis*, *E. cloacae*, *E. aerogenes*, *Ac. baumanni*, *K. pneumoniae*, *K. Kristinae*, *Ps. aeruginosa*, *Pr. mirabilis*, *Str. mitis*, *Str. agalactiae*.

Some researchers reported that despite very thorough skin disinfection, positive culture results were obtained in 48% of pockets right after their dissection and in 37% of cases right before the wound suture, whereas in cultures taken before the skin was disinfected, positive results were reported in 88.3% of cases [34]. Our study detected positive pocket cultures in 50.41% of patients with infections. Most of these patients had site symptoms including redness, warmth, swelling and pus discharge from the wound. Positive pocket cultures were found in 53.57% of PI patients and in 58.02% of LDIE+PI patients who made up 31.41% of all cases. Positive pocket cultures were found in 32.08% of LDIE patients who did not show any signs of infection in this site. These cultures were also dominated by CoN (63.16%) and *S. epidermidis* (48.87%, MRSE- 26.32%) as well as *S. aureus* (21.05%, MRSA-6.02%). One of the reports pointed out that CoNS, more than any other pathogen was responsible for pocket infections. It has been emphasized that CoNS was predominating in patients who underwent further repair procedures or had more leads, including infective ones, implanted in cardiovascular system. Present study showed that CoNS, more often than S.aureus was found in patients with leads left in their hearts (36.84% *vs.* 7.14%). The same applies to patients with at least three leads (31.58% *vs.* 14.29%) and to those who underwent at least three surgeries (including implantation) (36.84% *vs.* 14.29%). However, more S.aureus related infections were detected after implantation (71.43% *vs.* 36.84%), but the differences were not statistically significant. Present study remains in compliance with other world reports and confirms the assumption that staphylococcus bacteria are mostly responsible for developing infections. Microorganisms which in normal circumstances constitute physiological bacterial flora of the skin lead to infections during implantation or device exchange or when the lead or generator box get outside as a result of skin injury and consequently the infection spread along the lead down to the right endocardium giving rise to lead related endocarditis. Sometimes those pathogenic microorganisms happen to be transmitted through blood vessels to the device pocket where they form biofilm on PM/ICD/CRT elements. Biofilm consist of individual bacteria accumulating and making up dense cultures which form multicellular structure covering biomaterials. It may originate from bacteria triggering infections coming from other systems which as the infection spreads through blood vessels finally reach the heart. Our study shows that patients with concomitant infections of skin, respiratory or urinary systems or neuroinfections are more susceptible to infective complications, especially to LDIE. Similar results were reported by other studies [35].

The reason why so many infections are caused by CoNS is that cardio-implants get easily contaminated during the surgery. These bacteria are most often found in operative area and adhere more easily than S.aureus to biomaterials. *S. aureus* tends to occur more often in patients undergoing a single surgical procedure when infection

developing within 12 months of the surgery. Similar results were reported by other researchers who also underlined that *S. aureus* was detected mainly in patients with concomitant disorders. Immune deficiency prompts the development of *S. aureus* infections, and this is way these infections tend to have much more severe course [18,36-38].

Conclusions

1. Fever and concomitant infections predominated in the clinical picture of LDIE.

2. In patients with infections, especially LDIE, CRP appeared critical to diagnostic results.

3. Transesophageal echocardiography proved more efficient at diagnosing LDIE than transthoracic examination.

4. *Staphylococcus epidermidis* and *Staphylococcus aureus* seem to be most often causes of infective complications. They normally make up physiological flora of the skin and mucous membranes, which points out that infections are of endogenic origin.

5. *S. epidermidis* infections developed after more than 12 months of the surgery whereas *S. aureus* took less than 12 months.

Conflict of Interest

The authors declare that they have no conflict of interest.

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