Review paper

Enterococcus faecalis as a cause of infective endocarditis – systematic review of case reports

Enterococcus faecalis jako przyczyna infekcyjnego zapalenia wsierdzia – przegląd systematyczny opisów przypadków

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Key words: systematic review, *Enterococcus faecalis*, infective endocarditis.

Słowa kluczowe: przegląd systematyczny, *Enterococcus faecalis*, infekcyjne zapalenie wsierdzia.

Abstract

Introduction: *Enterococcus* bacteria account for nearly 10% of infective endocarditis (IE), making it the fifth most common cause. Many cases of enterococcal IE have been described.
Aim of the research: To systematically review these case reports and try to find common features characterising IE caused by E*nterococcus faecalis*.
Methods: In December 2022, the PubMed, EBSCO, and OVID databases were searched. The final analysis included 28 publications yielding data on *E. faecalis* IE, taken from 89 reported cases.
Results and conclusions: The systematic review revealed an enhanced mortality rate due to multiple organ failure in patients with prosthetic valves and numerous comorbidities. The presence of an artificial valve was associated with an atypical course of *E. faecalis* IE. This was similar in patients who had a history of cancer. Moreover, it was observed that *E. faecalis* IE in people < 60 years old was mostly associated with either an atypical presentation or another disease manifestation.

Streszczenie

Wprowadzenie: Bakterie z rodzaju *Enterococcus* odpowiadają za prawie 10% przypadków infekcyjnego zapalenia wsierdzia (IZW), co czyni je piątą pod względem częstości przyczyną tego schorzenia. W dostępnym piśmiennictwie opisano wiele przypadków enterokokowego IZW.
Cel pracy: Systematyczny przegląd opisów przypadków i próba znalezienia wspólnych cech charakteryzujących IZW wywoływane przez *Enterococcus faecalis*.
Metody: W grudniu 2022 roku przeszukano bazy PubMed, EBSCO i OVID. Do ostatecznej analizy włączono 28 publikacji zawierających opisy 89 przypadków IZW, którego przyczyną był *E. faecalis*.
Wyniki i wnioski: Systematyczny przegląd opisów przypadków wykazał zwiększoną śmiertelność z powodu niewydolności wielonarządowej u pacjentów ze sztucznymi zastawkami i licznymi chorobami współistniejącymi. Ponadto obecność sztucznej zastawki była powiązana z nietypowym przebiegiem IZW o etiologii *E. faecalis* u pacjentów. Podobnie było u pacjentów z historią nowotworową. Stwierdzono też, że IZW wywołane przez *E. faecalis* u osób poniżej 60. roku życia było najczęściej związane z nietypowym przebiegiem lub z manifestacją innej jednostki chorobowej.

Introduction

Enterococcus faecalis belongs to the abundant *Enterococcus* genus, and is a gram-positive, aerotolerant, spherical or oval bacteria that can exist singly or form pairs, chains, or groups. The most important characteristics of *E. faecalis* are persistence and high adaptability, allowing it to survive in harsh environmental conditions [1, 2]. It is a widespread bacterium in the environment, and it also occurs as a natural coloniser of the gastrointestinal tract of humans and animals. However, it should be remembered that it has pathogenic potential, especially due to its surface proteins, with adhesin function, which are associated with the initial adherence of bacteria and subsequent formation of a biofilm [3–5]. The above features enable the bacteria to trigger infections, including neonatal infections, infections of the urinary tract, abdominal and pelvic cavities, also prosthetic joints, as well as more invasive infections of the circulatory system, such as bacteraemia and infective endocarditis (IE) [3, 6, 7].

A natural feature of *E. faecalis*, as well as the entire *Enterococcus* genus, is reduced susceptibility to

many antimicrobial agents, including β-lactams. The bacteria are resistant to almost all cephalosporins, anti-staphylococcal penicillins, and aztreonam. *In vitro*, *E. faecalis* is susceptible to carbapenems, while there are few clinical data regarding their use in humans [3, 8]. Enterococci are also resistant to other antibiotics including clindamycin, trimethoprim/sulfamethoxazole, and to clinically achievable concentrations of aminoglycosides. The susceptibility of the *Enterococcus* genus to tetracyclines and erythromycin is not used clinically due to widespread acquired resistance to these antibiotics. They may be susceptible to vancomycin; however, emerging resistance genes to this antibiotic among the *Enterococcus* genus have been reported. Furthermore, enterococci rapidly acquire resistance to newly introduced antibiotics, such as linezolid or daptomycin, although most remain susceptible to them [9–11].

Infective endocarditis is a disease that develops as a result of infection of the endocardium with bacteria or fungi. The vegetations most frequently affect the heart valves, but can also appear in the ventricles, atria, or on foreign bodies present in the heart, such as pacemaker leads [12]. IE is characterised by high morbidity and mortality, as indicated by recent data showing that the annual incidence of IE is about 3–10 for every 100,000 people per year, whereas mortality reaches up to 30% within 30 days of the onset of the first symptoms [13–16].

Streptococcus spp. and *Staphylococcus* spp. are the most frequent aetiological factors, together representing more than 70% of cases of IE. Another group are enterococci with an IE-causing frequency of 9%, among which *E. faecalis* constitutes 90% of cases [17]. The remaining aetiological factors of bacterial IE include bacteria from the HACEK group (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.), fungi (*Candida* spp., *Aspergillus* spp. or *Histoplasma capsulatum*), polymicrobial infections, and there are also cases in which bacteria do not grow from blood cultures (Figure 1) [16, 18].

Infective endocarditis is twice as common in men as in women, with a prevalence primarily in the elderly between 60 and 80 years old, but it can also occur in other population groups (Figure 2) [19–21]. Patients most often have multiple comorbidities including diabetes, chronic heart disease, chronic kidney disease, or cancer [13, 16, 22]. An increased risk of IE has also been noted in patients with degenerative valve disease, having a prosthetic valve, an implanted cardiac device, patients who have undergone surgery in the past few months, or those who have taken intravenous drugs [23, 24].

Patients are very often dismissive of the first manifestations and therefore may not visit the doctor for a prolonged period, thinking that the symptoms will soon subside. By the time they finally present themselves to the physician, they most frequently report

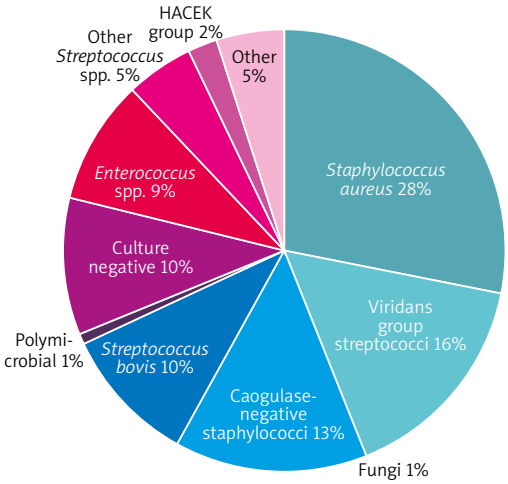

Figure 1. Microbiological aetiology of infective endocarditis in Europe (HACEK group = *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella* spp., and *Kingella* spp.) [16, 18]

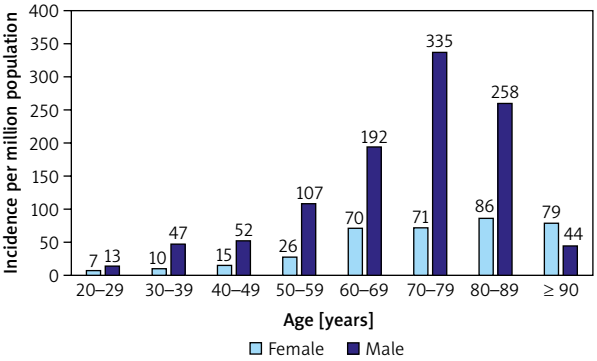

Figure 2. Prevalence of infective endocarditis in relation to age and sex [20]

the sudden onset of fever, generalised muscle and joint pain, malaise, weight loss, or breathlessness [17, 25–27]. In some cases, endocarditis may manifest as skin lesions including rash, petechiae, or the classic but rare diagnostic signs of Osler's nodules, Janeway lesions, or Roth spots on the eye fundus [12]. Some patients may be asymptomatic and then present to the doctor with complications of IE, such as myocardial infarction or stroke [15].

The symptoms of IE are nonspecific and remarkably similar to much more common inflammatory or infectious diseases, thus presenting difficulties during diagnosis and occasionally causing patients to be treated for another disease entity [17]. This is associated with increased time to diagnosis of IE and can contribute to an enhanced risk of complications of the disease, which may include fatal outcomes [28–30]. Therefore, results from microbiological analysis, laboratory tests, and diagnostic imaging are needed to establish the diagnosis. All the above are components

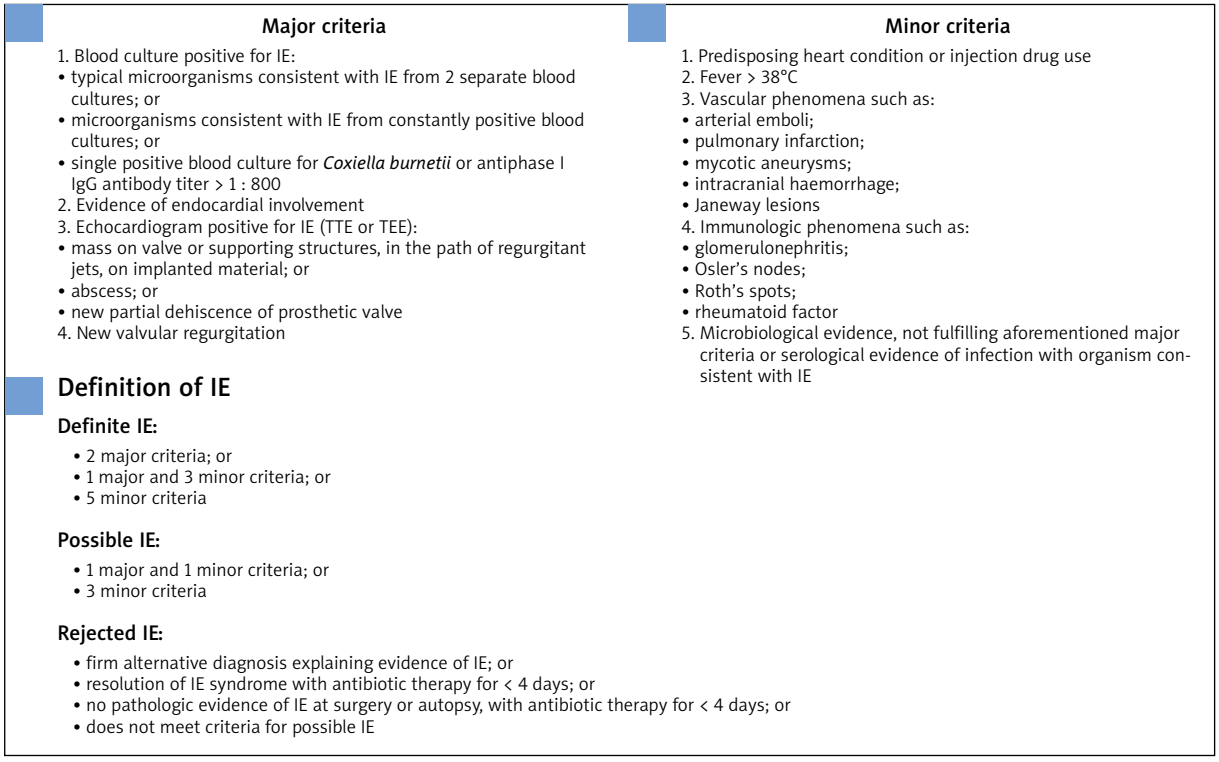

Figure 3. The modified Duke criteria for infective endocarditis (IE – infective endocarditis, TTE – transthoracic echocardiography, TEE – transoesophageal echocardiography). Based on Li *et al.* [31] and Prendergast [32]

needed to diagnose IE through the clinically modified Duke diagnostic criteria (Figure 3) [31, 32]. However, it should be remembered that these criteria were created for classification for scientific research and not as a diagnostic tool for clinicians; hence, the limitations in their use in patients with suspected prosthetic valve endocarditis, right-sided endocarditis, and infections of implanted cardiac devices [12, 33].

Aim of the research

The main purpose of this systematic review is to compile case reports of patients with *E. faecalis*-related IE and to determine whether the results of physical examination, laboratory tests, and imaging examinations for the diagnosis of IE tended to corelate with the patients' features.

Methods

Criteria for considering studies for the review

Only case reports (CRs) that were published entirely in English were included in this review. CRs were considered for inclusion if they were based on papers of a patient with IE and with *E. faecalis* as the primary cause of the presenting complaints. We also considered reports describing cases of patients treated in an atypical and different manner than proposed in guidelines for this condition. Cases in which the manifestation of endocarditis was presented with atypical symptoms or by another disease entity were also included.

Search methods

The search was conducted up to December 2022 in the following databases, with no restriction on either publication year or publication status:

- PubMed (https://pubmed.ncbi.nlm.nih.gov), (Access on 28 December 2022),
- EBSCO host (https://search.ebscohost.com), (Access on 28 December 2022),
- OVID (https://ovidsp.ovid.com), (Access on 28 December 2022).

The following search strategy was used for the PubMed database: "ALL = infective endocarditis AND enterococcus faecalis AND case report". The same strategy was also applied to the EBSCO host database and OVID.

Restrictions were applied to the language in which the CR was published. CRs that contained the entire text in English were considered, while those containing only an abstract in English were rejected. On the other hand, all the CRs were included regardless of the country from which they originated.

The authors also scanned the references of all relevant articles.

The titles and abstracts identified through the search process were reviewed by the authors. This

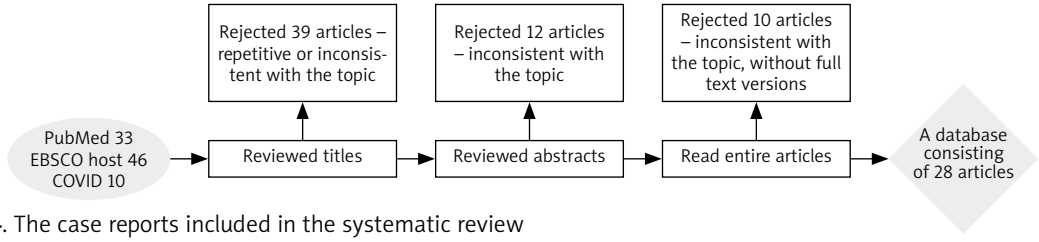

Figure 4. The case reports included in the systematic review

was followed by retrieving the full texts of selected CRs and evaluating them for eligibility.

Results

The search results were summarised in the flow diagram in Figure 4, and the articles included in the systematic review are listed in Table 1.

Of the 231 publications identified, 89 were potentially suitable for this systematic review. Then, 61 articles were excluded: 43 due to inappropriate research methods (the articles were incompatible with the search topic), 15 due to repetition of articles between databases, and 3 due to inability to access the full text of the CRs. The final analysis included 28 publications yielding data on *E. faecalis* as a cause of IE, taken from 89 reported cases.

Discussion

Through analysis of the reviewed CRs [34–61], men were more often affected by IE than were women (in 18 out of 28 CRs). The disease was observed mostly in the age group between 60 and 80 years. As many as 18 patients, both male and female, were in this age range according to the gathered CRs. However, in 3 cases IE was diagnosed in patients under the age of 40 [38, 46, 54]. Unfortunately, in some cases, it was impossible to identify the gender and age of the patient [35, 52].

According to the CRs, patients presented to the physician or emergency room with a variety of symptoms, of which the most common were fever, chills, shortness of breath, cough, or generalised fatigue [34–38, 40, 43–45, 49, 51–57, 60]. In general, these are non-specific symptoms that do not allow a straightforward diagnosis but are recurrent enough in most patients to suggest that further diagnostics should also be directed toward IE. On the other hand, there have been patients in whom symptoms were absent for a prolonged period [34, 45] or appeared with sudden blindness [39, 48], soreness in the joints [40], acute pain and numbness in the leg [46, 56, 61], or various forms of skin lesions [43, 47]. In the case of the 64-year-old patient [50], these lesions appeared as erythema, erosions with scales, and crusts on the face and upper part of the thorax. The patient had a skin sample taken for histopathological examination, which led to a diagnosis of pemphigoid. However, the lesions did not respond to treatment, and due to persistent inflammatory parameters, further diagnosis was pursued. It was eventually found that the pemphigoid appeared secondary to IE. Sometimes the first symptom was a complication of IE, which was manifested as acute coronary syndrome with ST-segment elevation [51, 52], or weakness of the left side of the body in a patient with stroke [41, 59]. In the case presented by Labbe *et al.* [56] the complication of IE was also a stroke, which manifested as word-finding problems and moderate headaches that persisted for more than 1 week. Interestingly, the patient had a previous history of deep vein thrombosis diagnosed 6 weeks before the current hospitalisation. In another case [61], a 63-year-old man sustained sudden dysphasia and hemianopia following a stroke. In the aforementioned 2 cases, the CT scan revealed multiple minor brain infarcts caused by septic embolism.

When comparing patients with IE, several of them had diseases such as hypertension, dyslipidaemia, obesity, or diabetes [35–37, 40, 41, 45, 51, 60]. Three out of 28 cases had comorbid chronic kidney disease [34, 42, 60]. For some patients, among the concomitant diseases was cancer, either in remission or currently undergoing treatment [37, 39, 48, 51, 56, 60], while most patients did not have coexisting illnesses or were not mentioned in the CRs [38, 43, 44, 46, 50, 52, 55, 59]. Based on the physical examination, in some cases it has been possible to establish the probable cause of developing an *E. faecalis* infection; however, in up to 70% of patients it is not possible to identify the main cause of the infection [56]. The most common cause of *E. faecalis* infection was due to the formation of vegetations on the pacemaker wires or prosthetic valves [41, 45, 50, 52, 57]. Because of the presence of *E. faecalis* in the gastrointestinal microbiota, infections also came from lesions of the colonic mucosa – a small perforation in the rectal area [51], or a previous polyp removal [53]. For the 63-year-old man, the first symptom of IE was rapidly progressing heart failure and lower extremity pain, which appeared several weeks after dental treatment [61]. In addition, chronic urinary tract inflammations and transurethral surgeries predisposed to bacteraemia with the aetiology of *E. faecalis* [42, 43]. Moreover, in the case of an 80-year-old patient, regular catheterisation due to an enlarged prostate led to micro-injuries through which bacteria entered the general circulation and subsequently be-

Table 1. Characteristics of case reports included in the systematic review

References	Gender	Age	Valve prosthesis on admission	Treatment	Outcome
[34]	Female	70	Absent	Ampicillin	Valve replacement
[35]	Unknown	Unknown	Absent	Ampicillin with ceftriaxone	Valve replacement
[36]	Male	75	Absent	Ampicillin with ceftriaxone	Death due to multiple organ failure
[37]	Male	80	Absent	Ampicillin with ceftriaxone	Diffuse alveolar haemorrhage
[38]	Female	31	Absent	Ampicillin with gentamicin	Valve replacement
[39]	Male	77	Absent	Amoxicillin with gentamicin	Endogenous intraocular inflammation
[40]	Male	59	Absent	Penicillin G with gentamicin	Valve replacement
[41]	Male	52	Absent	Ampicillin with gentamicin	Stroke, valve replacement
[42]	Female	68	Present	Ampicillin with gentamicin	Multiple organ failure, death due to septic shock
[43]	Male	82	Absent	Amoxicillin with gentamicin	Stroke, rupture of aneurysm secondary to IE
[44]	Female	42	Absent	Ampicillin with gentamicin	Full recovery without complications
[45]	Male	68	Absent	Vancomycin with gentamicin	Surgical treatment, full recovery
[46]	Female	36	Absent	Daptomycin with gentamicin	Full recovery without complications
[47]	Male	65	Absent	Amoxycillin with gentamicin	Full recovery without complications
[48]	Male	53	Absent	Vancomycin	Stroke
[49]	Male	75	Absent	Ampicillin with gentamicin	Full recovery without complications
[50]	Female	64	Present	Ampicillin with ceftriaxone	Pemphigus foliaceus, death due to aortic valve rupture
[51]	Female	69	Absent	Ampicillin with ceftriaxone	Multiple organ failure, death due to cardiogenic/septic shock
[52]	Unknown	64	Present	Amoxicillin with ceftriaxone	Death due to multiple organ failure
[53]	Male	69	Absent	Vancomycin with gentamicin	Full recovery without complications
[54]	Male	38	Present	Unknown	Valve replacement
[55]	Male	63	Absent	Penicillin G with gentamicin	Full recovery without complications
[56]	Male	59	Absent	Penicillin G with gentamicin	Valve replacement
[57]	Female	51	Absent	Vancomycin	Full recovery without complications
[58]	Male	80	Present	Ampicillin with ceftriaxone	Full recovery without complications
[59]	Male	75	Absent	Vancomycin with ampicillin	Death due to septic shock
[60]	Male	67	Absent	Ampicillin with gentamicin	Valve replacement
[61]	Male	63	Absent	Penicillin G with ceftriaxone	Removal of mycotic aortic aneurysm, valve replacement

came the cause of this patient's IE [58]. However, there were also completely different cases, as in the case report of Tamura *et al*. [38], in which the patient developed IE as a result of a caesarean section performed 3 months earlier, or as presented in the case report of Nishanth *et al*. [44], in which the patient's repeated blood transfusions led to the development of 2 vegetations on the pulmonary valve.

Regarding the laboratory test findings, the most frequent deviations from normal were increased levels of C-reactive protein and white blood cells [34, 37, 38, 40, 45, 47, 49, 51, 53, 55, 57, 60]. In addition, some patients had decreased haemoglobin levels and elevated platelet parameters [37, 38, 40, 44, 47, 56, 60]. Only in 1 case, the panel of tests was expanded to include rheumatoid factor, which was necessary to confirm the diagnosis of IE according to the modified Duke criteria [37]. Patients first had their blood drawn for cultures, which were essential both for the diagnosis of bacteraemia and its aetiological agent. Unfortunately, negative cultures have also been reported [34, 35, 57], and then only imaging examinations could be used, which also turned out to be unsuccessful in 1 case of a 70-year-old female patient [34]. The patient developed acute mitral valve insufficiency, which was treated surgically. The vegetation on the mitral valve was found only intraoperatively, and blood cultures performed after surgery grew *E. faecalis*.

When diagnosing IE, imaging examinations are important. Most commonly, transthoracic echocardiography (TTE) is performed, which is a simple and readily available method to visualise vegetations on the heart valves. This technique is often adequate to make the diagnosis of IE [35, 38, 39, 41, 43–45, 47, 59]. Nevertheless, in some cases, TTE is insufficient or requires confirmation, and then transoesophageal echocardiography (TEE) is additionally performed. This method is more sensitive and specific, thus significantly increasing the chance of detecting vegetations on the valve [36, 40, 46, 49, 51, 53–55, 58] as well as other changes characteristic of IE including abscess [42, 50, 54], or pseudoaneurysm and aneurysm [48, 50]. In the case report presented by Bourlond *et al*. [52], none of the imaging modalities were able to visualise the valve lesions, and only post-mortem examination revealed the presence of multiple vegetations on the prosthetic aortic valve. When the above-mentioned imaging examinations become insufficient, and it is not possible to detect lesions on the valves or within the pacemaker leads with their assistance, then 18F-FDG positron emission tomography computed tomography (PET/CT) may be used. This method was used in the case of a 51-year-old woman [57] in whom, despite symptoms suggestive of IE, both blood cultures and echocardiography failed to detect the disease. At that time, 18F-FDG PET/CT was used, which revealed increased bacterial uptake of glucose

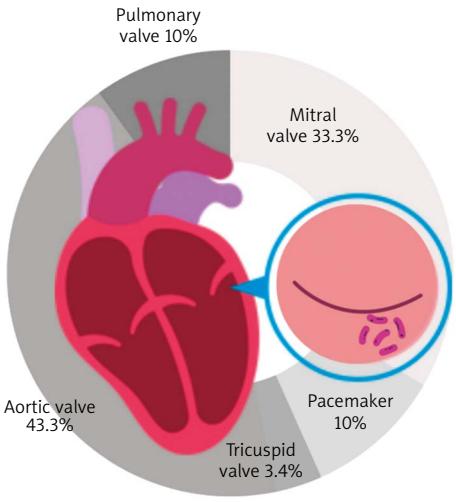

Figure 5. Percentage distribution of *Enterococcus faecalis* vegetation location in cases of infective endocarditis

along the pacemaker electrode pathway, including additionally the right ventricle and the device pocket.

In patients who developed IE, the vegetations most often occupied the left side of the heart, i.e. the changes were situated primarily on the aortic valve and followed by the mitral valve [34, 36–43, 46, 48–54, 56, 58–61]. Out of the 28 CRs reviewed, they were present in 13 and 10 cases, representing 43.3% and 33.3%, respectively. Among them, in 1 case, both these valves were simultaneously involved [40]. The pulmonary valve was next in order of involvement in IE, being affected in 3 out of 28 cases, accounting for 10% [35, 44, 53]. Of these, there was a case in which both the aortic and pulmonary valves were simultaneously affected [53]. Only in 1 case was the tricuspid valve occupation observed [47], which is an unusual localisation for IE, especially if the patient has no factors predisposing to this, such as the use of intravenous drugs. In the case described by Wilczynska *et al*. [47], the patient presented to the doctor with back pain and a lumbar rash, and the medical history revealed that he had symptoms of lumbar spondylosis in addition to concomitant ischaemic heart disease. In contrast, there was no history of previous surgical procedures or chronic urinary tract infections, and all possible sources of *E. faecalis* infection were ruled out during hospitalisation. Hence, the presence of vegetation on the tricuspid valve was not a surprise to the attending physicians and was associated with the extended time required to diagnose IE. The last 3 cases [41, 45, 57] were related to the presence of vegetations on the pacemaker leads. While 2 patients presented with numerous comorbidities, the third patient, a 51-year-old woman, only suffered from postpartum cardiomyopathy [57]. The localisation of IE *E. faecalis* vegetations are summarised in Figure 5.

The lesions, occurring on the valves, are the reason for their damage, resulting in their regurgitation. This condition has been observed in nearly every case, re-

gardless of the type of valve involved [34–53, 55–61]. An exception was a case reported by Buggey and Hoit [54], wherein a patient with a previous history of intravenous drug use, as the complication of prosthetic aortic valve insufficiency, presented stenosis. In addition, the patient was observed to have perivalvular thickening, which at surgery was found to be due to abscess formation and dehiscence. If the valves were severely damaged and caused significant myocardial overload, manifested by increasing dyspnoea and prompt fatigue of patients, then they were replaced with prosthetic valves [35, 36, 38, 40, 41, 56, 60, 61].

Currently, 2 methods are recommended for the treatment of IE caused by *E. faecalis*: the combination of a β-lactam with an aminoglycoside and the use of a double β-lactam [62]. These methods are considered the standard of treatment based on *in vitro* experimental data and multiple case series. In the first method, the preferable β-lactam is penicillin or ampicillin in combination with gentamicin, and this treatment is recommended, although with the duration of therapy it is associated with a high risk of nephrotoxicity, especially in the elderly. Such treatment was used in 9 out of 28 patients [38, 40–42, 44, 49, 55, 56, 60]. The double β-lactam method uses the synergistic effect of ampicillin with ceftriaxone, whereby ampicillin leads to partial saturation of penicillin-binding proteins (PBPs) 4 and 5, while ceftriaxone leads to complete saturation of PBPs 2 and 3. This leads to a marked impairment of cell wall synthesis and exerts a synergistic bactericidal effect against *E. faecalis*. It has similar effectiveness to the aforementioned method and is recommended for patients with an increased risk of nephrotoxicity and HLAR strain infection. The risk of inducing *E. faecalis* resistance to vancomycin and *Clostridioides difficile* infection is a disadvantage of the therapy. This treatment modality was used in 6 out of 28 patients [35–37, 50, 51, 58]. In other cases, treatment variants were used with amoxicillin instead of ampicillin [39, 43, 47, 52]. In cases with an allergy to β-lactams or increased resistance to them, vancomycin [45, 53] or daptomycin [46] was included. In 2 cases, vancomycin alone was used in the treatment of IE [48, 57].

Infective endocarditis is a burdensome disease, and patients with IE were exposed to an additional risk of developing various types of severe complications. These manifested, as already mentioned, by myocardial infarction [51, 52] or stroke [41, 43, 51, 56, 59, 61]. The disease also unusually appeared as diffuse alveolar haemorrhage [37]. Complications can be associated with the detachment of embolic material from the vegetation, located on the valve or pacemaker electrodes, creating a septic embolism. Depending on where it is transported with the blood, it may cause a wide range of complications that manifest as the previously mentioned stroke, pain in the lower extremities resulting from a thrombus in the popliteal artery and superficial femoral artery [46], or by causing mycotic aneurysms in various regions of the body. In 2 out of 28 cases reviewed, the complication of IE was the development of a mycotic aneurysm in the distal superior mesenteric artery [43] presenting with severe abdominal pain and nausea, and a very rare case of a mycotic aneurysm in the aortic bifurcation into the common iliac arteries [61]. Despite the diagnosis of IE and the inclusion of appropriate treatment, some patients developed multiple organ failure in the course of septic shock, or acute renal insufficiency and sudden heart failure. These conditions have unfortunately been associated with fatal outcomes [36, 42, 51, 52, 59].

Conclusions

Infective endocarditis occurs especially in the elderly. They have an increased susceptibility to serious systemic infections due to numerous comorbidities, such as chronic kidney disease, chronic heart disease, diabetes, or cancer. Additionally, they have naturally reduced immunity with age, or among others because of treatment with glucocorticosteroids. The systematic review of the reported cases revealed an enhanced mortality rate due to multiple organ failure in patients with prosthetic valves and numerous comorbidities. Furthermore, the presence of an artificial valve was associated with an atypical course of IE in patients. This was similar in patients who had a history of cancer or were undergoing treatment at the time of hospitalisation. Moreover, it was observed that IE in people under 60 years of age was mostly associated with either an atypical presentation or manifestation as another disease entity.

Infective endocarditis, despite advances in diagnosis and microbiological techniques, remains a severe condition that, if untreated, can be life-threatening for the patient. Although the symptoms are nonspecific, which does not allow a direct diagnosis, a rudimentary echocardiogram should be performed in any such case to exclude the presence of valvular lesions in the heart. The clinicians should be even more vigilant if the patient reports a history of malignancy or prosthetic valve replacement. It is also important to pay attention to individual patient characteristics and the risk of serious consequences of IE when making treatment decisions.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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