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New ESC Guidelines for the management of endocarditis — opinion of clinician expert

Nowe zalecenia ESC dotyczące leczenia infekcyjnego zapalenia wsierdzia w opinii eksperta-klinicysty

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Abstract

As usual, at the end of the summer, the European Society of Cardiology (ESC) published a new recommendation. This year new "ESC Guidelines for the Management of Endocarditis" are available. The main changes in 2023 in comparison to the 2015 year are new recommendations for the necessity of Endocarditis Team introduction in hospitals, new definition of endocarditis, important changes in antibiotic therapy and some recommendations for cardiosurgery treatment of prosthetic valve endocarditis. The extraction of infected cardiac implantable electronic devices (CIED) and reimplantation of new CIED are also described in new guidelines. The transoesophageal echocardiography (TOE) is now an obligatory examination in patients with endocarditis. A few imaging techniques as computed tomography, nuclear imaging, and magnetic resonance are involved in infective endocarditis diagnosis with high class and level of recommendation. Recommendations for antibiotic prophylaxis in patients with cardiovascular diseases at increased risk of infective endocarditis are described. Patients with implanted ventricle assist devices are included in prophylaxis either. In the following article new recommendations with short clinical commentary are presented.

Key words: ESC recommendations, infective endocarditis, transesophageal echocardiography, computed tomography, isotope studies, magnetic resonance imaging, antibiotic therapy of IE, surgical treatment of IE.

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Introduction

As usual, new recommendations from the European Society of Cardiology (ESC) came out at the end of summer 2023, this time also concerning the management of infective endocarditis (IE). This paper aims to highlight the new recommendations and the modifications made compared to the previous 2015 version. In addition to changes in the wording of the recommendations, some of them have changed the class and level of reliability of the data. Assessing the new recommendations as a whole, it can be said that, in general, some of the recommendations have been refined (e.g. the creation of the Endocarditis Team) and definitions have been clarified to facilitate their use in diagnostic and therapeutic practice.

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Infective endocarditis group

One of the important and currently refined recommendations of the ESC is the establishment of an Endocarditis Team (ET), in Polish referred to as the "IE Group", i.e. a team of specialists for the treatment of IE [1]. The benefits of such a team have been confirmed in observational studies [2–7, 8–12]. The main tasks of the ET are to streamline the diagnostic process, assess any complications that may occur, and determine the best antibiotic therapy and the optimal timing of surgical intervention [1]. From a clinical point of view, these are extremely important tasks and actions to be carried out in every patient with suspected and already diagnosed IE. Due to the severity, complexity and varied course of the disease, recommendations and management should be selected individually for each patient and the composition of the ET should be as interdisciplinary as possible. Depending on the hospital's credentials, the composition of the ET team will vary [1]. A hospital/Centre with a department of valvular heart disease and cardiac surgery, with a full range of investigations and diagnostic and therapeutic capabilities should have a team of specialists as listed in Table 1.

In hospitals and centres without cardiac surgery, the internal medicine physician treating a patient with IE should consult with an infectious disease specialist or an internal medicine specialist with experience in the treatment of infectious diseases and a microbiologist. It is advisable to have a physician with experience in valvular disease and diagnostic imaging on the team to provide initial and subsequent echocardiographic assessments. An important and emphasised element is the cooperation between a centre with less diagnostic and therapeutic capacity and a centre with higher referral and broader diagnostic and therapeutic capacity especially in case of failure of antibiotic therapy and/or the occurrence of complications, which should result in the transfer of the patient to such a centre. Cooperation between centres is also an educational element and will improve the diagnostic and treatment process in the future [1]. The recommendations on the role of the Endocarditis Team in the early diagnosis of complicated cases of IE and collaboration between a higher and lower referral centre are Class I recommendations and Level of Evidence B, and this is a major change from the 2015 recommendations when the recommendations were Class and Level IIaB. The creation of an ET team, regardless of the centre's credentials, is one of the most important recommendations of the 2023 guidelines.

Diagnosis of infective endocarditis

In the new standards, the role of transoesophageal echocardiography (TOE) has been strengthened. The recommendations recommend TOE not only in suspected IE and a negative or non-diagnostic transthoracic echocardiogram (TTE) but also in patients with suspected IE and an implanted prosthetic valve or intracardiac device. The recommended wording "TOE is also recommended with an already confirmed diagnosis of IE on transthoracic examination, except for isolated right ventricular IE on a natural valve provided the TTE examination is of good quality and

Table 1. Composition of the specialist Endocarditis Team [1].

Basic composition	Additional specialists
Cardiologists[a]	Radiologist and medical specialist nuclear
Specialists in diagnostic imaging[b]	Pharmacist
Cardiac surgeons and surgeons/cardiologists removing infected CIEDs[d]	Neurologist[c] and neurosurgeon
Infectious disease specialist (or internal medicine specialist with experience in treatment of infections)	Nephrologist
Microbiologist	Anaesthesiologist[e]
	Intensive care physician[f]
Specialist in parenteral antibiotic therapy administered in the out-of-hospital setting	Multi-specialist team for cases addictions
	Geriatrician
	Social worker
	Nurses
	Pathomorphologist

[a]In centres with higher referral additionally doctors experienced in treatment of patients with heart failure, valvular heart disease, and interventional cardiologists, [b]among specialists in imaging diagnostics are also cardiologists/echocardiographists with skills of performing and interpretation of transoesophageal echocardiography, [c]from clinical point of view neurologist is the very important ET member especially when neurological complication are present and which are often the first symptoms of IE, [d]in Poland infected cardiac implanted electronic devices are also removed by experienced electrophysiologists, [e]anaesthesiologists experienced in cardiac patients treatment, [f]actually in Poland is a growing number of physicians with intensive therapy speciality

Table 2. Diagnostic recommendations in IE for suitability and indications for testing

Recommendation	class	level
Cardiac CTA is recommended in patients with suspected IE on native valves to detect valve lesions and for confirmation of the diagnosis.	I	B
Cardiac CTA is recommended in IE on native and prosthetic valves to diagnose IE if the echocardiographic result is inconclusive.	I	B
[18F]FDG-PET/CT(A) and cardiac CTA are recommended for suspected IE on prosthetic valves to detect valve lesions and for confirmation of the diagnosis.	I	B
[18F]FDG-PET/CT(A) for consideration in suspected CIED-associated IE to confirm the diagnosis.	IIa	B
CNS and whole-body imaging with CT, [18F]FDG-PET/CT and/or MRI are recommended in symptomatic patients with IE on native and prosthetic valves to detect peripheral lesions or additionally small IE criteria.	I	B
SPECT/CT with labelled leukocytes should be considered in patients with a high clinical probability of IE on prosthetic valve if ECHO is negative or inconclusive and when PET/CT is not available.	IIa	C
CNS and whole-body imaging with CT, [18F]FDG-PET/CT and MRI in IE on native and prosthetic valves can be considered as screening for the diagnosis of peripheral lesions in asymptomatic patients.	IIb	B
MRI or PET/CT is recommended in patients with suspected vertebral body and intervertebral space inflammation (spondylodiscitis) and osteomyelitis of the spine as complications of IE.	I	C
TTE/TOE is recommended to exclude IE in patients with vertebral body and intervertebral space inflammation (spondylodiscitis) and/or septic arthritis with positive cultures for pathogens typical of IE.	I	C

CTA — computed tomography angiography, CT — computed tomography, [18F]FDG-PET/CT(A) — 18F-fluorodeoxyglucose positron emission tomography/computed tomography, CNS — central nervous system, ECHO — echocardiography, IE-infectious endocarditis, PET/CT — positron emission tomography/computed tomography, MRI — magnetic resonance imaging; SPECT/CT — single photon emission tomography/computed tomography, TTE/TOE — transthoracic echocardiography/transesophageous echocardiography

the findings are unequivocal" changed the class of recommendations from IIaC in 2015 to IC in 2023 [1]. Now the recommendation is to perform a TOE in stable patients before switching from intravenous to oral antibiotic therapy (class IB). A TTE performed even by an experienced doctor on good echocardiographic equipment has several limitations, such as the imaging conditions depending on the patient's anatomy, the possibility of correct positioning of the patient for the examination, the presence of, for example, implanted prosthetic heart valves, implanted intracardiac electrodes and post-operative modifications to cardiac structures. Although in clinical practice the TOE examination has a fundamental role in the diagnosis of IE, it is still not common practice to perform transoesophageal examinations [13]. It is a test that is both conclusive for the diagnosis and exclusion of suspected IE. In confirmed IE, performing TOE allows a complete assessment of the cardiac structures involved in the infectious process, including determining the size and morphology of the bacterial vegetations, illustrates perivalvular leaks, abscesses, dislodgement of implanted prosthetic valves, as well as perforations of valve leaflets and fistulas between cardiac cavities. All these findings confirm the complicated course of IE and are an additional indicator for accelerated surgical management. Three-dimensional echocardiography also appears to have a significant place in the diagnosis of IE and its complications [1].

In the 2023 guidelines, recommendations have emerged to extend diagnosis with new imaging techniques. The recommendations in this area and the class and level of evidence are summarised in Table 2. The sanctioning and expanded recommendations for imaging studies are an important element in the often difficult diagnosis of IE (Table 2). Previous recommendations mentioned imaging studies as helpful in diagnosis but did not give them as high a grade of recommendation as they are now. In clinical practice, such examinations were performed on suspicion of IE and listed in the diagnostic criteria, but now their role in diagnosis has significantly increased through their availability and their explicit placement in the criteria for the diagnosis of IE (Table 3). The same was true for complications and sequelae of infective endocarditis, which have now been supplemented by osteoarticular inflammatory lesions previously not included in IE definition (Table 3) [1]. The ESC's proposed updated and clearer algorithm for diagnosing IE based on expanded and updated clinical-bacteriological criteria and imaging findings will significantly facilitate and accelerate the diagnosis of IE.

Antibiotic therapy

In the new ESC recommendations, antibiotic therapy has been modified. Even more attention has now been paid to the nephrotoxicity of aminoglycosides and ways of avoiding

Table 3. Criteria for the diagnosis of infective endocarditis [1]

Large criteria
1. Positive blood cultures: • In 2 separate blood cultures, pathogens typical of IE: oral *streptococci*, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group bacteria[a], *S. aureus, E. faecalis* • Pathogens typical of IE in positive blood cultures: • ≥ 2 positive blood cultures from samples taken > 12 h apart • all of 3 or most of ≥ 4 separate blood samples (including first and last one ≥ 1 h apart) • A single positive blood culture for *Coxiella burnetii* or the presence of phase I IgG antibody titre > 1:800 2. Imaging studies — confirming IE: anatomical and metabolic lesions characteristic of IE on native/prosthetic valves, perivalvular lesions and those present on artificial materials, detected by the following imaging studies: • TTE and TOE • CT of the heart • [18F]-FDG-PET/CT(A) • SPECT/CT using labelled leukocytes
Small criteria
1. Predisposing factors (high or intermediate risk factors e.g. history of IE, prosthetic valves, heart failure, mechanical heart assist devices, RHD, non-rheumatic degenerative valve disease, congenital heart valve defects, CIEDs, hypertrophic cardiomyopathy, parenteral drug addiction) 2. Fever > 38°C 3. Disseminated embolism including asymptomatic found only in imaging studies • Large systemic embolisms/infarcts and abscesses • Haematogenous, joint and bone septic complications • Mycotic aneurysms • Ischaemic and haemorrhagic complications in the CNS • Conjunctival haemorrhages • Janeway symptom[b] 4. Immunological symptoms: • glomerulonephritis • Osler nodules[c], Roth spots[d] • rheumatoid factor 5. Microbiological confirmation: • positive blood cultures that do not meet the large criteria • serological confirmation of active infection with pathogens typical of IE
Criteria for the diagnosis of IE
Confirmatory IE • 2 large criteria • 1 large and at least 3 small • 5 small Suspicion of IE • 1 large and 1 or 2 small criteria • 3–4 small criteria Excluded IE • On admission, no criteria confirmed or suspected IE with or without a confirmed alternative diagnosis.

[a]HACEK — genus *Haemophilus, Aggregatibacter-formerly Actinobacillus*; *Cardiobacterium, Eikenella* and *Kingella*; [b]Janeway symptom — small, painless lesions placed on hands and feet of erythematous or haemorrhagic nature; [c]Osler nodules — red-purple, slightly raised, often with a pale centre are late and rare skin symptom of IE existing on the fingers and feet caused by immune complexes deposition; [d]Roth spots — petechiae on retina. [18F]-FDG-PET/CT(A) — 18F-fluorodeoxyglucose positron emission tomography/computed tomography; CIED — cardiac implanted electronic devices; CNS — central nervous system; CT — computed tomography; IE — infective endocarditis; RHD — rheumatic heart disease; SPECT/CT — single photon emission tomography/computed tomography; TTE/TOE —transthoracic echocardiography/transesophageous echocardiography

or limiting their administration, all the more so because acute renal failure (AKI) is common in IE for a number of reasons, including peripheral embolism, haemodynamic disturbances due to heart failure or organ sequelae of generalised infection. Renal damage during aminoglycoside treatment may be irreversible [14, 15]. It has been shown that the combination of ceftriaxone and ampicillin can be used in IE with *Enterococcus faecalis* aetiology instead of an aminoglycoside with good effect, regardless of whether the strains are HLAR (high-level aminoglycoside resistance) or non-HLAR [16]. This combination of antibiotics has a better safety profile due to a significantly reduced risk of nephrotoxicity [16]. It is implemented in practice as a treatment of IE caused by bacteria of the genus *Enterococcus* [1].

Aminoglycosides are not recommended in treatment of native valve endocarditis (NVE) caused by staphylococci as there has been no demonstrated clinical benefit from their use, only increased nephrotoxicity [16–18]. When aminoglycosides are indicated in infections with other bacteria, e.g. resistant strains of oral *streptococci*, the duration of treatment should not be longer than 2 weeks [1]. When administering high/maximal doses of gentamicin, guidelines recommend determining the drug concentration once a week and assessing renal function. Although few centres can determine the concentration of antibiotics other than vancomycin, renal function monitoring is possible everywhere. Irrespective of the ESC recommendations, it is clinically and practically safe to monitor renal function more than once a week and not only when administering high doses of the drug. The recommended gentamicin concentration values for intravenous administration of the drug in a single daily dose should be < 1 mg/L (before the drug dose) and approximately 10–12 mg/L one hour after its administration [1].

Another aspect of IE treatment is the problem of bacterial drug tolerance. This is not typically antibiotic resistance, but a recurrence of infection after withdrawal of treatment. Pathogens that are characterised by slow growth or are dormant show phenotypic tolerance to most antimicrobial drugs except rifampicin [1]. Most often, such pathogens are found in vegetation or settle on artificial materials to form antibiotic-resistant biofilms, e.g. in IE on prosthetic valve endocarditis (PVE) [19]. The administration of rifampicin should be limited to infections involving implanted foreign bodies, such as PVE. The inclusion of rifampicin is not recommended until 3–5 days after other effective antibiotics have been implemented and bacteremia has already been cleared [1]. In staphylococcal PVE, ESC guidelines recommend the addition of rifampicin regardless of the susceptibility of the strains to this antibiotic and despite current studies questioning the benefit of such management [1, 20]. When using rifampicin, it is important to bear in mind the potential for the drug to damage liver cells, which can cause hepatitis and liver failure. Therefore, liver enzymes and bilirubin must be monitored frequently.

Recommendations for the treatment of staphylococcal and enterococcal infections include daptomycin. The drug should be administered in combination with a β-lactam or fosfomycin. This treatment is intended to increase the efficacy of antibiotic therapy and reduce the risk of developing bacterial resistance. Fosfomycin, on the other hand, is an old-generation drug, until recently rarely used, mainly orally in the form of single low doses (3g) in the treatment of urinary tract infections, and now often, as a drug of last resort, given intravenously in high doses (8–12g/day) and not only in IE but also in bacteraemia.

The treatment time for IE on prosthetic valves has been extended to as long as ≥ 6 weeks, and in IE on native valves, the treatment time has been set at 2–6 weeks [1]. The rules for antibiotic treatment after valve replacement surgery for prosthetic valves are clearly defined. Treatment is to be the same as that started before surgery, i.e. the same as that implemented with a native valve, and the duration of antibiotic treatment in both NVE and PVE is calculated from the first day of a negative blood culture, if previously positive. No treatment time is set from the day of surgery. A new countdown of antibiotic treatment time is justified when positive valve cultures are obtained [1].

The antibiotic susceptibility of pathogens was determined according to the EUCAST 2022 recommendations and categorised into three groups according to the accepted cut-off points for minimum inhibitory concentrations (MICs) [1]. The first group is pathogens susceptible to antibiotics at standard doses, i.e. therapeutic success should be achieved at these doses. The second group is also susceptible, but at increased doses of antibiotics and there is a high probability of achieving treatment success with increased exposure of the pathogen to the drug or with increased drug concentration at the site of infection. The third group are antibiotic-resistant pathogens and there is a high probability of drug ineffectiveness even with increased doses. Antibiotic exposure is defined as a component of elements such as the mode of antibiotic administration, dose, dose intervals, duration of intravenous drug infusion, and the extent of drug distribution and penetration affecting pathogens at the site of ongoing infection. It is the responsibility of the local microbiology laboratory to use appropriate diagnostic methods and provide criteria for interpreting the results obtained, and supervise the qualitative control of MIC results. Physicians are responsible for modifying and selecting the dose of antibiotics and the mode of administration to ensure optimal drug action [1].

The authors of recommendations ESC emphasise that the antibiotic recommendations have been developed based on results from clinical and cohort studies in patients

with IE or bacteraemia while stipulating, that current systematic reviews of large databases containing data from trials indicate low-quality scientific evidence evaluating both the benefits and side effects associated with the use of particular treatment regimens, which does not allow both to endorse as and to reject any antibiotic regimen for IE [1, 21, 22]. It should be borne in mind that regardless of the recommended regimens, which are the basis of therapeutic decision-making, it may be that positive blood cultures obtained with pathogen sensitivity determinations will verify antibiotic therapy. Detailed antibiotic recommendations for individual pathogens in the new recommendations are as follows [1]:

1. For oral *streptococci* and *Streptococcus gallolyticus*, there is no change in the antibiotic recommendations compared to 2015 this also applies to antibiotic therapy for β-lactam sensitisation. For two-week treatment (not applicable to PVE, and complicated NVE), the management is as in the 2015 standards except for the withdrawal of the recommendation for netilmicin anyway, the drug is currently unavailable.
2. In the treatment of methicillin-susceptible *staphylococci* in NVE, cloxacillin or flucloxacillin (the latter is not available in Poland, used in other countries) are used as before or cefazolin, which is new compared to previous recommendations. A similar change applies to PVE, here too, the alternative choice to cloxacillin is cefazolin, which is given in combination with rifampicin and gentamicin, with cefazolin with rifampicin for at least six weeks and gentamicin for two weeks. The following treatment regimens have been presented for patients allergic to β-lactams:

— For patients allergic to penicillins in NVE and PVE, cefazolin is recommended; vancomycin was previously used but proved to be an inferior antibiotic to β-lactams. In endocarditis on prosthetic valves cefazolin in combination with rifampicin and gentamicin. The recommendations described belong to class IB.
— The recommendation of class IIbC i.e. as a possible option to consider is combination therapy with daptomycin and ceftaroline or daptomycin and fosfomycin. For PVE, additionally rifampicin and gentamicin.

3. The same class of recommendations, i.e. IIbC, included a proposal to consider an antibiotic combination for the treatment of NVE caused by methicillin-resistant *staphylococci* consisting of daptomycin and, in addition, cloxacillin or ceftaroline or fosfomycin. It is recommended to administer daptomycin in a single high dose, i.e. 10 mg/kg/d *i.v.* [1].

In class IB, the previously present recommendation for vancomycin in infection with methicillin-resistant *staphylococci* remains. In severe infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin, daptomycin ceftaroline and dalbavancin are often the only effective antibiotics [1]. Daptomycin is an antibiotic registered for the treatment of endocarditis involving right heart structures and for bacteraemia that has been caused by *Staphylococcus aureus*. Daptomycin is at least as effective as vancomycin in the treatment of infections caused by *Staphylococcus aureus* and coagulase-negative *staphylococci* (CoNS), and in bacteraemia caused by MRSA with a high MIC for vancomycin (> 1 mg/L), its administration is associated with a better prognosis compared to vancomycin [23, 24]. Other alternatives for the treatment of IE due to MRSA include fosfomycin with imipenem, ceftaroline, quinupristin-dalfopristin with or without β-lactams, β-lactams with oxazolidinones i.e. with linezolid, β-lactams with vancomycin and large doses of trimethoprim with sulfamethoxazole, possibly clindamycin. Unfortunately, evidence of treatment efficacy has been obtained in studies on small populations of treated patients, so the antibiotics mentioned are not part of routine management and their administration should be consulted with ET and approved on a case-by-case basis [1].

Staphylococcus aureus infections are difficult to treat and often cause destructive cardiac damage, and vegetations are the cause of non-cardiac septic complications including stroke and splenic abscesses in left-sided IE, as well as pneumonia and lung abscesses in right-sided IE [25, 26]. The problem is not only the effectiveness of antibiotic therapy but also the treatment of complications, as well as the choice of the appropriate timing of surgery. On the one hand, the timing of the operation should be such that the extracardiac septic complications are sufficiently treated not to become a source of recurrent IE and dislodgement of the replaced valve (common with early surgery in *Staphylococcus aureus* infection) and, on the other hand, take into account the presence of possible haemodynamic abnormalities such as pulmonary oedema or cardiogenic shock, which are indications for urgent or emergency surgery [1]. In making such surgical decisions, the consultations within the ET created will certainly be helpful.

Patients with IE on a native valve caused by bacteria of the genus *Enterococcus* sensitive to β-lactams and without a high-level of aminoglycoside resistance (non-HLAR *Enterococcus spp.*) should be treated with a combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks or with gentamicin applied for 2 weeks [1]. The same antibiotic therapy for non-HLAR *Enterococcus spp.* infection is also recommended in IE on an prosthetic valve and in complicated endocarditis on a native valve or with symptoms lasting > 3 months. Both recommendations listed have a recommendation class of IB. In NVE and PVE caused by *Enterococcus* type HLAR, a combination of ampicillin or amoxicillin with ceftriaxone for 6 weeks is recommended (class IB recommendation). In patients with IE caused by β-lactam-resistant *Enterococcus spp.* vancomycin for 6 weeks and gentamicin for 2 weeks is recommended

(class IC). If vancomycin resistance is present then the recommended drug combination is daptomycin with β-lactams such as ampicillin, ertapenem, ceftaroline or fosfomycin (IC class).

When IE is suspected to be caused by Gram-negative bacteria from the group HACEK (genus *Haemophilus, Aggregatibacter-formerly Actinobacillus, Cardiobacterium, Eikenella* and *Kingella*), for which difficulties in microbiological diagnosis are typical, the microbiology laboratory should be alerted to the need for a specially devised test scheme. These bacteria are characterised by slow growth. Standard MIC assessment may be unreliable. Some of the bacteria in the HACEK group produce β-lactamases. This is a reason to forgo treatment with ampicillin as a first-line drug. They remain sensitive to ceftriaxone and other third-generation cephalosporins and fluoroquinolones. The proposed treatment is ceftriaxone given for 4 weeks in NVE and 6 weeks in PVE. If the bacteria do not produce β-lactamases, ampicillin can be used for 4–6 weeks with gentamicin used for a fortnight. Ciprofloxacin is a much less well-documented alternative treatment [1].

In IE caused by Gram-negative but non-HACEK bacteria, the recommended treatment is early surgery with prolonged up to six weeks of combination treatment consisting of β-lactams and aminoglycosides with the addition of quinolones or cotrimoxazole [27, 28]. *In vitro,* microbiological testing combined with assessment of serum antibiotic concentrations can help determine appropriate treatment and its efficacy. An important part of treatment due to the severity of infections and the rare occurrence of these pathogens is to discuss patients within the Endocarditis Team [1].

Blood culture-negative infective endocarditis (BCNIE), refers to a situation in which bacterial growth in blood cultures fails using routine microbiological methods. This may be due to the administration of antibiotics before blood culture collection. It is important to take blood cultures before administering antibiotic therapy. This is not only important in suspected IE but in any other suspected serious infection. Despite the use of special culture media for patients already receiving antibiotics, which are designed to eliminate the effect of the antibiotic administered, bacterial growth is not always achieved. Even the first few doses of the drug can inhibit bacterial growth and thus make it significantly more difficult to identify the aetiology of IE. To identify the pathogen, it may be necessary to discontinue antibiotics and re-take blood cultures, but this is only possible in stable patients, receiving antibiotics for a short time and without obvious local or generalised complications [1]. Negative blood cultures are observed for fungal aetiologies of IE, as well as for slow- and difficult-growing bacteria requiring specific conditions and substances for growth. Such bacteria are referred to as fastidious bacteria. The demanding bacteria also include the HACEK group. For some pathogens, serological tests can be helpful. This applies in particular to bacteria such as *Coxiella burnetii*, strains of the genera *Bartonella* and *Brucella*, fungi of the genus *Aspergillus,* and the bacteria *Mycoplasma pneumoniae* and *Legionella pneumophila* [1]. Genetic tests, which include polymerase chain reaction (PCR), can also be helpful in diagnosis. Genetic testing is useful in the diagnosis of *Tropheryma whipplei*, the genus *Bartonella* and fungi of the genera *Candida* and *Aspergillus* [1]. In patients with prosthetic heart valves and BCNIE, molecular testing using fluorescence *in situ* hybridisation (FISH) in combination with PCR of the 16S rRNA gene subunit and its sequencing (FISHseq) can complement classical diagnostics of bacterial cultures. FISHseq improves the diagnosis of PVE in 30% of cases by complementing conventional bacterial identification obtained by microbiological cultures and identifies the pathogen in 35% of negative valve cultures. FISH also informs PVE severity and status by determining their activity, contribution to biofilm formation, and presence on artificial materials [29]. A diagnosis of non-bacterial PVE should always be considered in the case of negative results of microbiological tests. The gold standard for the diagnosis of IE is histopathological and microbiological examination of infected tissue or thrombus fragments removed during surgery [1].

In the treatment of BCNIE, there are generally no optimal treatment regimens and the duration of treatment is often difficult to determine [1]. Treatment of BCNIE caused by *Tropheryma whipplei,* for example, is highly empirical and very long. Antimicrobial efficacy has been described for long-term treatment, i.e. > 1 year. If the CNS is involved in the infectious process, sulfadiazine should be added to the proposed doxycycline. Alternatively, ceftriaxone for 2–4 weeks or penicillin G and streptomycin for 2–4 weeks followed by oral cotrimoxazole [1]. Infection of fungal aetiology is often found in drug-dependent patients, in immunocompromised patients and in PVE. The predominant genera are *Candida* and *Aspergillus*. Due to the high mortality rate of more than 50%, antifungal treatment should be combined with surgery [30]. For the treatment of infections caused by the genus Candida, high-dose echinocandins and liposomal amphotericin B with or without flucytosine are used [1]. For Aspergillus infections, the treatment of choice is voriconazole, possibly in addition to echinocandins or amphotericin B [30]. If long-term treatment (sometimes lifelong) is required oral azoles (fluconazole, voriconazole) are used [30]. Unfortunately, there are no clear criteria as to the duration of antifungal treatment in IE and such therapeutic dilemmas are encountered in clinical practice. When treating patients with fungal IE, it is advisable to use the opinions of the Endocarditis Team including experts in the treatment of infectious diseases.

Before the results of blood cultures are available, the treatment of IE will be empirical and should be undertaken

as soon as possible. The following factors need to be considered when determining antibiotic therapy: history of recent antibiotic therapy, type of endocarditis i.e. on native vs. prosthetic valve, if on prostethic then early vs. late PVE and type of infection i.e. out of hospital vs. hospital-acquired (HAI) [1]. The choice of antibiotic therapy should also take into account the local epidemiological situation including recognised antibiotic resistance of bacteria. In NVE and late PVE, antibiotics should be selected to cover the spectrum of *staphylococci*, *streptococci* and *enterococci*. In patients with a previous history of antibiotic therapy, antibiotics other than those previously used should be given. The presence of CoNS as a causative agent of IE should be considered in the treatment of PVE but not NVE. Early PVE or HAI endocarditis should be treated to include methicillin-resistant *staphylococci*, *enterococci* and optimally non-HACEK Gram-negative bacteria. Within 24–48 hours of pathogen identification, antibiotic therapy should be changed to targeted therapy [1]. Proposed empirical antibiotic therapy regimens are in recommendation class IIaC and IIbC [1, 32].

Invasive treatment

New guidelines also present recommendations for the surgical and invasive treatment in IE. In early PVE i.e. revealed up to 6 months after surgery, reoperation with valve replacement and infected tissues removal is recommended (IC) [1]. In PVEs classified as early high risk of death is observed and antibiotic therapy rarely or even at all does not guarantee the recovery of IE [31].

In IE caused by infection of CIED as soon as possible, during the initial, empirical antibiotic therapy, remove of the implantable electrical device in its entirety is recommended (IB) [1, 32]. The in-hospital or 30-day mortality rate in CIED infection is 5–8%, and the use of antibiotic therapy alone without removal of the pacemaker increases it sevenfold [32]. Higher mortality in CIED is also influenced by delayed removal of the infected pacing system [32, 33]. A 2020 expert document from the European Heart Rhythm Association (EHRA) recommends the removal of the infected CIED preferably within three days of the start of hospitalisation. The EHRA document also recommends simultaneous removal of vascular ports and chronically retained haemodialysis catheters [32]. Once the CIED has been removed, it is recommended that indications for device reimplantation be considered, especially as between 13 and up to 52% of patients no longer require reimplantation of a permanent cardiac electronic implantable device [32–35]. In the case of indications for permanent implantation of a new CIED, consideration should be given to choosing a device type other than those removed, e.g. a subcutaneous defibrillator (S-ICD), epicardial device or a leadless pacemaker (LPM) rather than devices with intracardiac leads [32]. In patients who will require protection until a permanent implantable device is re-implanted, e.g. because of pacing dependency, the risk of sudden cardiac arrest (SCA) from dangerous ventricular arrhythmias or the likelihood of significant heart failure after loss of resynchronisation, temporary replacement therapy should be planned. If the removed CIED was a pacemaker only, then in pacing-dependent patients temporary pacing is to be considered as a bridge to pacing system reimplantation, e.g. using a permanent intracardiac pacing lead connected to a permanent pacemaker but routed externally [32]. In patients at risk of SCA until the implantation of a new cardioverter/defibrillator, it is recommended to use a defibrillation waistcoat [32]. The biggest problem, however, is the removal of a pacemaker with a resynchronisation function. Often, either immediately after the removal of such a pacemaker or a few hours after the procedure, symptoms of acute heart failure develop. Patients may miss the IC class recommendation, which states that reimplantation of the CIED is recommended at a site distant from the first i.e. infected, and the time of implantation should be postponed as late as possible and the following conditions must be met: repeat blood cultures taken after removal of the device in a patient without vegetations must be negative for at least 72 hours, and if there are vegetations then repeat blood cultures must be negative for at least two weeks (IC) [1, 32–35]. Of course, patients receive antibiotic therapy and have intensified treatment for heart failure. However, none of the cited studies provide a ready prescription for the treatment of such patients when pharmacological treatment for heart failure fails. In my opinion, in haemodynamically unstable patients, the use of temporary cardiac support, e.g. with an IABP, may be justified on vital indications. From other hand, implantation of an IABP in a generalised infection, as with the presence of any foreign body, may increase the risk of recurrence or chronicity of the infection.

Prevention

The 2023 standards introduced updated recommendations for the prevention of IE. Indications for antibiotic administration include oral and dental procedures in patients: at high and intermediate risk of IE and in patients with implanted mechanical heart assist devices (recommendation class IC), and antibiotic prophylaxis remains to be considered in heart transplant patients (recommendation class IIbC) [1]. In patients at high risk of IE, systemic antibiotic therapy may be considered for invasive diagnostic and therapeutic procedures involving the lungs, gastrointestinal tract, urogenital tract, skin or muscle (IIbC). Optimal aseptic preparation of the skin before CIED implantation is an obvious procedure recommended in the recommendations as infection prevention (IB). Standard surgical aseptic procedures are recommended before insertion and manipulation of intravascular

catheters in cardiac catheterization laboratory (IC). Antibiotic therapy including *Enterococcus* and *Staphylococcus aureus* pathogens remains to be considered before TAVI and other endovascular valve procedures (IIaC) [1].

Conclusions

- Expanded criteria for the diagnosis of IE increase the chance of a correct and rapid diagnosis.
- The participation of imaging studies and the empowerment of TOE in the diagnosis of IE is a validation of the current diagnostic procedure and the introduction of these studies into daily routine medical practice.
- The establishment of an Endocarditis Team, an interdisciplinary team comprising specialists from several specialities, through expert opinion, will make it possible to decide on the best course of treatment for the patient.
- Antibiotic recommendations have been varied for the treatment of certain pathogens causing IE. Older generation antibiotics have returned. The nephrotoxicity of aminoglycosides is highlighted and proposals are given to replace them in possible situations with drugs from another group.
- Antibiotic regimens were given based on the results of clinical and cohort studies conducted in IE.
- It is advisable to remove infected CIED devices in their entirety and as soon as possible after the diagnosis of IE.
- Valve reoperation is necessary in early PVE.
- In addition to the need for aseptic skin preparation before CIED implantation procedures and before insertion of intravascular catheters, the ESC guidelines for the prevention of IE recommend systemic antibiotic prophylaxis before oral and dental procedures in patients at high and intermediate risk of IE and in patients with implanted mechanical heart assist devices and remains to be considered in heart transplant patients.

The above notes and comments on the 2023 recommendations mainly concern new or modified previous recommendations. Certainly, not all novelties and modifications made in the current ESC recommendations have been discussed. It is worth referring to the full text of the recommendations when treating specific patients with infective endocarditis.

Additional information

Author contribution
AK — 100%.

Conflict of interests
The author declare no conflict of interests.

Fnding
None declared.

Streszczenie

Jak zwykle pod koniec lata ukazały się nowe zalecenia Europejskiego Towarzystwa Kardiologicznego (ESC). W 2023 roku dotyczą one między innymi postępowania w infekcyjnym zapaleniu wsierdzia (IZW). W porównaniu do 2015 roku najważniejsze rekomendacje z 2023 roku to między innymi: zalecenie powołania w szpitalach zespołów ds. leczenia infekcyjnego zapalenia wsierdzia (*Endocarditis Team*), uzupełnione kryteria rozpoznawania IZW, istotne zmiany w dotychczasowej antybiotykoterapii, zalecenia co do leczenia operacyjnego wczesnego IZW na sztucznej zastawce oraz zalecenia co do usuwania i ponownego wszczepiania zakażonych elektrycznych urządzeń stymulujących (*CIED*). Obecnie obligatoryjnym badaniem również u chorych z już rozpoznanym IZW jest echokardiograficzne badanie przezprzełykowe. W diagnostyce zwiększono znaczenie wykonywania badań obrazowych takich jak tomografia komputerowa, badania izotopowe i rezonans magnetyczny. Dokonano również zmian w profilaktyce IZW. Dotyczą one chorych z wysokim i pośrednim ryzykiem IZW, a także chorych z wszczepionymi urządzeniami mechanicznie wspomagającymi pracę serca. Artykuł jest opatrzony krótkimi klinicznymi komentarzami dotyczącymi nowych rekomendacji ESC.

Słowa kluczowe: rekomendacje ESC, infekcyjne zapalenie wsierdzia, echokardiograficzne badanie przezprzełykowe, tomografia komputerowa, badania izotopowe, rezonans magnetyczny, antybiotykoterapia IZW, leczenie — zabiegowe IZW

Folia Cardiologica 2024; 19: 214–224

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