Endocarditis

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General introduction

Infective endocarditis

History

Infective endocarditis (abbreviated as "IE" or simply "endocarditis") is a serious disease. It was invariably fatal until three generations ago.[1] However, increasing knowledge enabled important advances in both diagnostic and therapeutic techniques. By the end of the 19th century there was a conceptual view of endocarditis and it was Sir William Osler who constructed a unified view of the disease.[1] In the beginning of the 1940s, antibiotics were for the first time used to treat endocarditis.[1] It resulted in some therapeutic success and provided the first clinical evidence that bacteria located in the endocardium could be targeted.[1] Despite the fact that historically, the vast majority of pathogens were susceptible to penicillin, initial treatment attempts were failing. This was due to the extremely high cost and limited supply of the drug. After penicillin became widely available in sufficient quantity and purity, safe administration of larger doses for longer periods of time became possible.[1] Subsequently, antibiotic therapy of endocarditis rapidly was a success and clinical experience accumulated.[1] Therefore, it was established in the 1960s that endocarditis was a curable disease.[1] However, since it was not possible to control the infection in cases that did not respond to the administered antibiotics, some thought about a direct intervention on the heart to remove the infectious process.[1] A group at Duke University understood that the removal of the infected valve and its substitution by valve prosthesis was a possibility to remove the cause of clinical illness, instead of it being a surgical risk.[1] Thus, cardiothoracic surgery was the second major breakthrough for reducing mortality of endocarditis, both by controlling the infection and repairing anatomical damage. Thereafter, in the 1970s, the visualization of vegetation by echocardiography was reported and it was once ageing Duke University who made an important contribution to our knowledge about endocarditis.[1] In the 1990s, they called for diagnostic standardization by inclusion of echocardiography as major criterion for disease.[1] Hereafter, echocardiography and blood culture started to gain identical diagnostic hierarchy as major criteria for the diagnosis of endocarditis, both with evident gain in sensitivity for diagnosis.[1]

Epidemiology

Nowadays, endocarditis is curable but still associated with significant morbidity and mortality.[2] During the acute phase of infection, current in-hospital mortality rates are reported in the range of 14-22%.[3-5] Furthermore, 1-year mortality approaches an average of 40%, with a large variation in different subpopulations.[3-5] The case-mortality rate of prosthetic valve endocarditis is reported to be even higher than of native valve endocarditis, ranging from 25-59%.[6] Also, 2-year mortality for cardiac device-related endocarditis is higher if the infected device is not removed, ranging from 31% to 66%.[7] Conversely, combined management consisting of complete device removal and antimicrobial therapy reduces this to 18%.[7] In general, patients require cardiothoracic surgery for direct source control and for acute complications in 25-50% of cases during the acute phase of infection, while 20-40% of patients require surgery later on to repair anatomical defects.[8]

Endocarditis is a medical issue because neither its incidence nor its mortality has decreased in the past

30 years.[2,9] The global incidence of infective endocarditis is estimated at 3-10 episodes per 100.000 person-years[2], meaning that at least 250 cases are diagnosed in the Netherlands each year.[10] This number is probably an underestimation as diagnosis of endocarditis is difficult and some patients remain undiagnosed. Guidelines on endocarditis are largely based on expert opinion resulting from the lack of data due to its relatively low incidence in the general population, its devastating nature, the subsequent absence of randomized clinical trials and the limited number of meta-analyses.[2] Affected patients therefore require a multidisciplinary and collaborative team approach.[11-14]

Clinical presentation

Patients with endocarditis may present with clinically highly variable signs and symptoms, with essentially any organ (and often multiple organs) that may be affected. The most important clinical symptoms and signs of endocarditis include fever (96%), heart murmur (85%), new murmur (48%), changing murmur (20%), hematuria (26%), vascular embolic event (17%), Osler's nodes (3%), splinter hemorrhages (8%), Janeway lesion (5%), splenomegaly (11%), Roth's spots (2%), and conjunctival hemorrhage, as found in more than 2700 patients with definite endocarditis.[15] Therefore, a low threshold for suspicion is required. Table 1 shows the most important clinical situations in which endocarditis should be considered and investigated.[2] Due to the unspecific signs and symptoms, the differential diagnosis for these patients is often broad.

1. A febrile illness and a murmur of new valvular regurgitation;
2. A febrile illness, a pre-existing at-risk cardiac lesion and no clinically obvious site of infection;
3. A febrile illness associated with any of:
    - Predisposition and recent intervention with associated bacteremia,
    - Evidence of congestive heart failure,
    - New conduction disturbance,
    - Vascular or immunological phenomena: embolic event, Roth spots, splinter hemorrhages, Janeway lesions, Osler's nodes,
    - A new stroke,
    - Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause;
4. A protracted history of sweats, weight loss, anorexia or malaise and an at-risk cardiac lesion;
5. Any new unexplained embolic event (e.g. cerebral or limb ischemia);
6. Unexplained, persistently positive blood cultures;
7. Intravascular catheter-related bloodstream infection with persistently positive blood cultures 72h after catheter removal.

Table 1: Clinical situations in which infective endocarditis should be considered and investigated according to the BSAC-criteria (British Society of Antimicrobial Chemotherapy).[16]

Infection of heart valves could lead to their dysfunction or even complete hemodynamic failure. Since functional heart valves are essential for a proper pumping activity of the heart, it is important that the heart valves are structurally sound. The close relationship between heart valve function and death partly explains the high mortality rate of this disease. Two other major mortality causes include disturbed conductance (e.g. atrioventricular conduction block) and complications in vital organs (e.g. cerebral embolization with or without infarction or major bleeding).

Pathogenesis

Infective endocarditis involves inflammation of the endocardium, the layer of endothelial cells covering the inside of the heart. Most frequently heart valves become infected in the course of the disease. The inflammation is caused by infection with microorganisms, most often a bacteria and occasionally yeasts (in 2-5% of cases).[15] Clearly, two steps are important in the development of infective endocarditis: 1) a nidus in the heart for the bacteria to attach and to start the infectious process, this can be damaged endothelium, intracardiac prosthetic material, or for *Staphylococcus aureus* presence of "only" inflammation[17,18]; 2) bacteria present in the blood that flows through the heart, which are able to attach to this nidus present in the heart. In case of damaged endothelium (Figure 1), first platelets and matrix proteins attach to the endothelium, forming sterile vegetation (thrombotic endocarditis). Hereafter, bacteria present in the bloodstream attach to this sterile mass, recruiting even more platelets and matrix proteins, and forming vegetation. The common feature of the growth state of attached microorganisms is that they develop a biofilm.[19] Biofilm is formed by the irreversible attachment and growth of microorganisms on a surface and the subsequent production of a conditioning film or coating of extracellular polymers of polysaccharides, (glyco)proteins and extracellular DNA in a 3 dimensional structure.[19] Biofilms can occur on living tissues such as the endocardium, but also on inanimate surface materials such as implanted medical devices.[20,21] A fundamental concept in the pathogenesis of implanted device infections is the formation of such biofilms by the infecting microorganism.[22] If endocarditis is related to implanted intracardiac prosthetic material, the infecting microorganism could have been introduced in two ways: primary, during the implantation of the prosthetic material; or secondary, via transportation of bacteria through the blood. After formation of biofilm by the attached bacteria, residing bacteria alter phenotype in comparison to their planktonic form which enables them to evade the host immune response and become resistant to antimicrobials.[22] These encased micro colonies of bacteria are also hard to culture.[23] Hence, biofilm-growing bacteria cause a large number of chronic infections resulting from their difficult diagnosis and eradication; these infections also share clinical characteristics such as persistent inflammation and tissue damage.[20,22,24,25]

Besides endocardial infection, other important steps in the pathogenesis of endocarditis are the spread of infection locally and through the rest of the body, as well as indirect effects resulting from the infection. This spread of infectious complications is possible through four mechanisms: 1) local spread, the local destruction of heart tissue by extension of the infectious process, causing the formation of paravalvular abscesses and pseudoaneurysms; 2) septic emboli, resulting from a chunk of the vegetation that gets lose, spreading through the blood to get stuck somewhere else in the bloodstream (e.g. cerebral infarction); 3) metastatic infection, resulting from bacteria spreading through the blood and attaching to another (preferential) site (e.g. vertebral osteomyelitis); 4) spread by circulating immune complexes and other immunopathologic factors, causing extracardiac sites of immunological complications (e.g. glomerulonephritis).

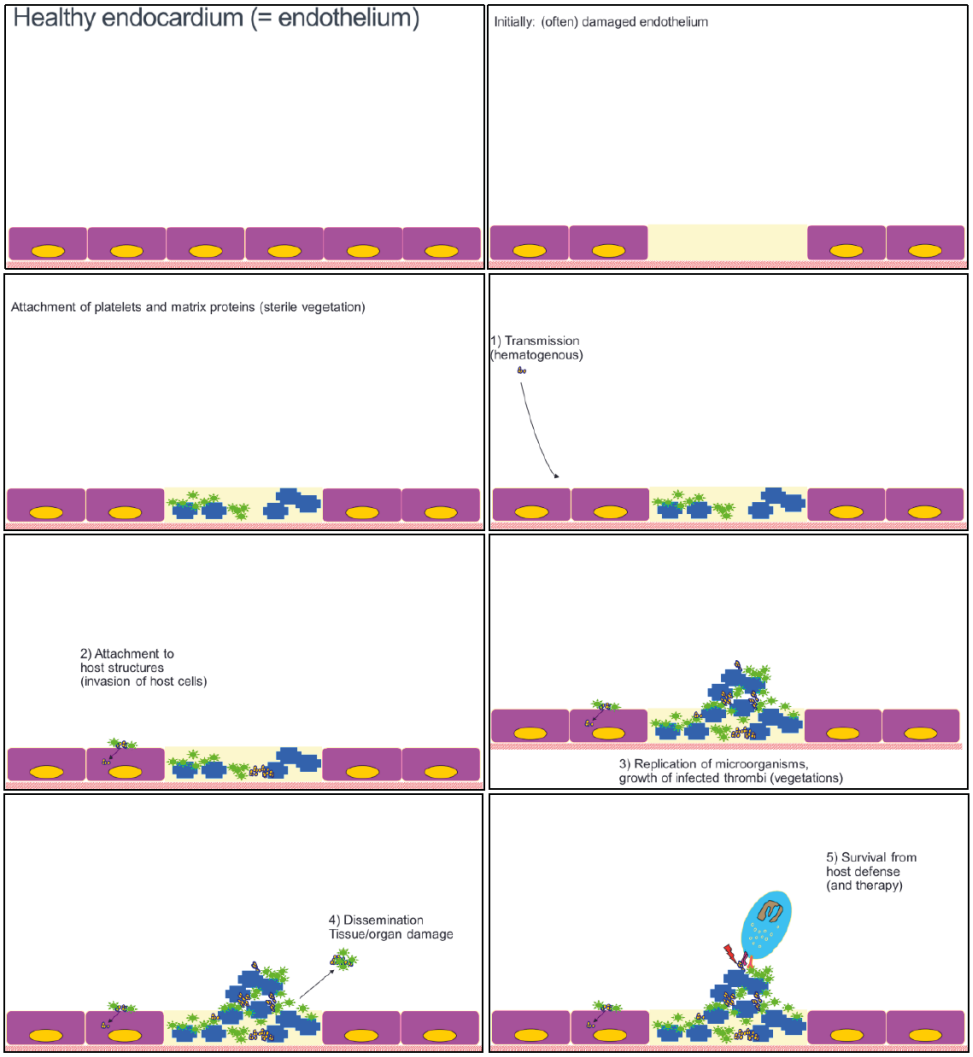

Figure 1: Pathogenesis of infective endocarditis. [Bhanu Sinha: personal communication - graphics adapted]

Pathogens

The pathogens causing infective endocarditis are a rather limited group of species (Table 2). It is more often caused by gram-positive than gram-negative bacteria.[26] Gram-positive bacteria are better able to adhere to host tissue, damaged valves and even anatomically intact endothelium. In addition, they better withstand host defense mechanisms (e.g. neutrophil granulocytes, complement-mediated bactericidal activity and T-lymphocytes).[15,26] Together, the gram-positive micro-organisms *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus spp.* are the responsible pathogens for more than 80% of all cases of disease.[26]

Micro-organism	Cases (%)
Staphylococcus spp.	42.1
Staphylococcus aureus	31.6
Coagulase-negative staphylococci	10.5
Streptococcus spp.	29.6
Viridans group streptococci	18.0
*Streptococcus bovis**	6.5
Other streptococci	5.1
Enterococcus spp.	10.6
HACEK group	1.7
Non-HACEK gram-negative bacteria	2.1
Fungi	1.8
Polymicrobial	1.3
Other species	3.1
Culture negative	8.1

Table 2: Most common etiologic agents, results from an international cohort of n=1778 patients with definite infective endocarditis.[15] *currently referred to as *Streptococcus gallolyticus*. HACEK = *Haemophilus parainfluenzae, H. aphrophilus* and *H. paraphrophilus* (currently referred to as *Aggregatibacter aphrophilus* and *A.paraphrophilus*), *H. influenzae, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*, and *Kingella denitrificans.* HACEK organisms are a group of fastidious, gram-negative bacteria found as etiologic agents for infective endocarditis. The group of "other species" includes *Propionibacterium acnes* (currently referred to as *Cutibacterium acnes*) among others. The culture-negative group also included pathogens such as *Tropheryma whipplei*, *Coxiella burnetii* (Q-fever), and *Bartonella* spp., which are not accessible by (standard) culture methods.

It is important to have an up-to-date epidemiological overview about the most common microbial causes of endocarditis (Table 3), both for prophylaxis and empirical therapy. The epidemiology of pathogens causing endocarditis changes throughout time, as streptococcal infections were most prevalent until the 1990s[27], opposing recent reports. In a systematic review about the most common microbial causes of 33.214 cases of infective endocarditis from 36 counties in the 21st century, found *Staphylococcus aureus* as most common microorganism in almost all population subgroups, but not in patients with implantable devices, prosthetic valves, immunocompromised non-HIV, and the subgroup from Asia.[28] Furthermore, methicillin resistant *S. aureus* (MRSA) was isolated in 4.5-51.1% of *S. aureus* cases.[28] Viridans group streptococci, coagulase-negative staphylococci, *Enterococcus* spp. and *Streptococcus bovis* were other common causes (Table 3).[28] These changes in the epidemiology of the pathogens causing endocarditis is due to a progressive evolution in risk factors, while classic predisposing conditions are less prevalent, new risk factors have emerged.[26]

Group (number of cases)	Most common pathogens
Europe (n=12.572)	*Staphylococcus aureus* | Viridans group streptococci | Coagulase negative staphylococci | *Enterococcus* species | *Streptococcus bovis*
Patient group	**Most common pathogens**
Pacemaker/ICD (n=505)	*Staphylococcus aureus* and Coagulase negative staphylococci (equal rates) | *Streptococcus pneumoniae* | *Enterococcus faecalis*
Dialysis (n=233)	*Staphylococcus aureus* | Coagulase negative staphylococci | Viridans group streptococci | *Pseudomonas aeruginosa*
Prosthetic valve (n=994)	Coagulase negative staphylococci | *Staphylococcus aureus* | Viridans group streptococci | *Enterococcus* species | *Streptococcus bovis*
Intensive care unit (n=228)	*Staphylococcus aureus* | Oral streptococci | Other Group D streptococci | *Enterococcus* species | Gram negative bacteria
Congenital heart defect (n=672)	Viridans group streptococci | *Staphylococcus aureus* | Coagulase negative staphylococci | *Streptococcus bovis* | *Enterococcus* species

Table 3: Most common pathogen in infectious endocarditis (as of 2016).[28]

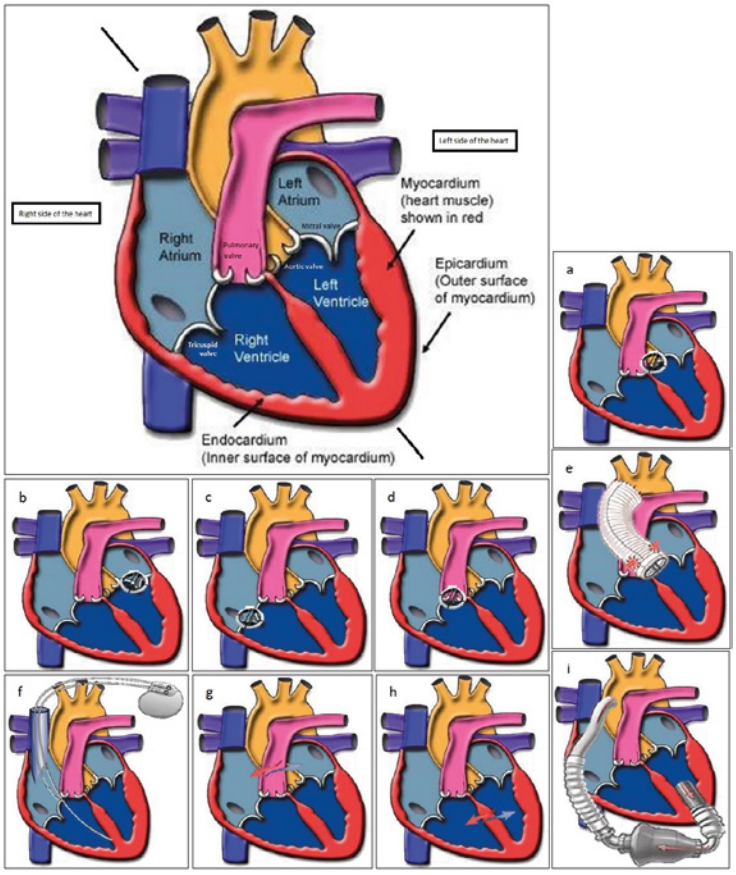

Figure 2: Schematic figure of the heart, featuring the epicardium, myocardium and endocardium, its right and left side, the atria and ventricles, and the four heart valves. In small panels are shown intracardiac prosthetic materials: a) prosthetic aortic valve, most commonly affected valve in endocarditis; b) prosthetic mitral valve, second most commonly affected; c) prosthetic pulmonary valve, third most commonly affected; d) prosthetic tricuspid valve, least commonly affected valve; e) prosthetic aortic valve with ascending aorta (Bentall procedure); f) pacemaker and ICD; g) patch to fix an ASD; h) patch to fix a VSD; i) left ventricular assist device.
[Figures adapted from Texas Heart® Institute, St. Jude Medical Inc., Cornily *et al.* Arch Cardiovasc Dis. 2010:103(3):170-5, Jansen J.M.J.F. 2006 website:verblijfopaarde.nl, Patkar R. video:youtube.com, cardiacsurgery.ucsf.edu]

Risk factors

A classic risk factor for endocarditis is rheumatic heart disease (causing damaged endothelium). Newer risk factors include congenital heart disease and degenerative valve lesions (both causing damaged endothelium), an *in situ* prosthetic heart valve, pacemaker, implantable cardioverter defibrillator (ICD), left ventricular assist device (LVAD), patch to fix an atrial septum defect (ASD) or ventricular septum defect (VSD) (all present intracardiac prosthetic material, Figure 2), intravenous drug use, and health care contact (all introducing bacteria intro the bloodstream, e.g. hemodialysis). An indirect risk factor is advanced age as it increases the possibility of the previously mentioned risk factors being present.

Intracardiac prosthetic material *in situ* is a common risk factor for developing endocarditis these days. Furthermore, implantation of intracardiac prosthetic material is increasing due to an ageing population and expanding indications for implantation. To substantiate this with figures, Kim *et al.* summarized available literature on pacemakers/ICDs from 1993 until 2008 and showed an increase for their rate of implantation with 96% and of infection with 210%.[29] As indicated with the mortality rates presented in the epidemiology section of this introduction, does the presence of intracardiac prosthetic material *in situ* importantly influence the decision making process when treating endocarditis. Furthermore, these figures show the major risk of fatal outcome if the infected device cannot be removed.

Prophylaxis

Transient bacteremia (or fungemia) may result in colonization of a predisposing cardiac nidus, which may lead to the development of infective endocarditis (Figure 1). Transient bacteremia occurs whenever a mucosal surface that is colonized with bacteria (or fungi) is traumatized, for example with dental extractions or other dental procedures and with gastrointestinal, urologic, or gynecologic procedures.[15] Also, every day activities such as brushing teeth and defecation cause us all to have transient non-clinical bacteremias repeatedly. The degree of bacteremia is proportional to the degree of trauma produced by the procedure and the degree of colonization of traumatized mucosa.[15] Furthermore, the micro-organisms isolated reflect the microbial flora of the traumatized mucosa.[15] The bacteremia usually is low grade (≤10 colony-forming units [CFU]/mL) and transient, which means that the bloodstream is usually re-sterilized within 15-30 minutes.[15]

For more than 50 years, prophylactic administration of antibiotic agents before procedures known to cause bacteremias was recommended to prevent endocarditis.[15] However, besides studies showing that this practice could prevent endocarditis in experimental animals *in vivo*, there is no definitive evidence for (cost-) effectiveness in humans.[15] Most prominently, the incidence of endocarditis appeared to be unaffected in countries recommending prophylaxis. To a large part, insufficient compliance, a changing resistance spectrum, and the creation of a false feeling of safety have been named as potential reasons. Furthermore, antibiotics can cause unwanted side effects. Therefore, recent American[30] and European[12] guidelines restrict this prophylactic use of antibiotics and limit it to patients at highest risk of an adverse outcome of endocarditis.[15] The recent European guideline restricts the patients at risk to three groups.[12] The first group consists of patients with any prosthetic valve, including a transcatheter valve, and those

in whom any prosthetic material was used for cardiac valve repair.[12] The second group consists of patients with a previous episode of endocarditis.[12] The third group consists of patients with congenital heart disease (CHD), further subdivided into those with any type of cyanotic CHD and those with any type of CHD repaired with prosthetic material (both placed surgically and by percutaneous techniques) up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains.[12] Conversely, in the United Kingdom, the National Institute for Health and Clinical Excellence (NICE), had recommended ending the practice of using antibiotics to prevent IE altogether.[31] They rather recommend instructing patients well and implementing early appropriate diagnostics (and therapy).

These days, there are contradicting reports about whether this major change in prophylaxis practice has resulted in an increased number of endocarditis cases.[15] Either way is education of patients at risk for endocarditis and their health care providers recommended. Furthermore, it is important to prevent health care–associated infections and treat them promptly in order to reduce the incidence of bacteremia's that could cause endocarditis. However, since preventive measures may fail, early diagnosis and prompt treatment of endocarditis are important to reduce morbidity and mortality.

Care for patients

It is important for patients and treating clinicians to know whether infective endocarditis is present or not (diagnosis), ensuring that adequate therapy can be started as early as possible. Therapy of infective endocarditis consists of high-dose and long-term intravenous antimicrobial therapy. A substantial proportion of patients require surgical resection of the infectious process and correction of any cardiac anatomical alterations to restore heart (valve) function as well. Early and accurate diagnosis of endocarditis is crucial, because a delay in adequate therapy, and thus incomplete eradication of infection, negatively affects outcome.[32,33] Furthermore, achieving an earlier and more accurate diagnosing of endocarditis could potentially lead to lower costs of hospitalization, by shortening hospital stay and avoiding complications of insufficient treatment and prolonged admission.[34] Mean hospital charge for endocarditis in general was reported to be as high as $122,204 in the US over 2008-2009,[35] and even $146,000 for device-related endocarditis specifically.[36] On the other hand, when the diagnosis of endocarditis is regarded unlikely already early in the diagnostic work-up of a patient suspected of endocarditis, the costs of additional evaluation and longer length of stay in the hospital can be avoided.[37]

Diagnosis

Unfortunately, despite the availability of increasingly more diagnostic tools, the diagnosis of endocarditis is still difficult as not one single test is able to tell with certainty whether a patient has endocarditis or not. Therefore, diagnosing endocarditis relies on performing multiple tests, all providing complementary information about different aspects of the disease. Ideally, a multidisciplinary team of experts discusses how to interpret the results of all these different tests in the unique setting of the individual patient thereafter.[11-14] This process largely involves assessing the risk for the presence of endocarditis or an alternative disease. Conversely, diagnosis of endocarditis is considered certain

only when appropriate specimens from surgery or autopsy reveal positive histology and/or culture (pathological Duke criteria).[38] But as these specimens are available only in a minority of patients, and nearly never *a priori*, the diagnosis of endocarditis in everyday clinical practice is based on a scoring system as reference method that allows for a standardized approach to clinical signs and symptoms, and laboratory, microbiological, and imaging tests, called the modified Duke criteria (clinical Duke criteria).[39] Since these criteria are acquired retrospectively, a diagnosis or exclusion of endocarditis at admission still carries a high amount of uncertainty.[40] Therefore, sensitivity and specificity of the modified Duke criteria are approximately 80%, when pathologically confirmed cases are considered as the gold standard.[41] This leaves a relatively high rate of false positive and false negative diagnosis for the total population at risk.[42] Thus, these criteria are to be used together with careful clinical judgment and follow up.[12,39]

The modified Duke criteria

The clinical Duke criteria to diagnose endocarditis involve both major and minor criteria (Table 4, showing the newest revision of the modified Duke criteria, including additional imaging modalities). The major criteria are evidence of endocardial involvement and positive blood cultures of sufficient quality and quantity. Evidence of endocardial involvement can be provided by imaging with echocardiography. Echocardiography is currently considered as a diagnostic cornerstone for endocarditis. It provides information about the functioning and anatomical situation of the heart chambers, walls, valves, vessels, as well as the flow of blood (by Doppler). Unfortunately, (two dimensional) echocardiography, either transmitted through the thorax (trans-thoracic, TTE) or the esophagus (transesophageal, TEE), may still miss vegetations and life-threatening complications in up to 30% of patients,[43-45] especially in patients with intracardiac prosthetic material.

Blood cultures are generally regarded as being of sufficient quality and quantity if a typical pathogen is isolated and the bacteremia is persistant.[38] However, there are several limitations. First, several sets of blood cultures need to be drawn which should be of sufficient volume and drawn prior to starting antimicrobial therapy and this is regularly accomplished inadequately. Second, bacteremia with typical pathogens for endocarditis can also be found in patients with an alternative focus of infection. Third, low grade pathogens that are usually considered contaminants are also able to cause endocarditis, especially in patients with intracardiac prosthetic material. Fourth, a number of micro-organisms cannot be cultured routinely or are difficult to culture. And finally, blood cultures often remain negative in patients with previous antibiotic use, in the presence of biofilm and in primarily paravalvular disease (e.g. abscesses), most importantly in infection of prosthetic materials.[23,46-49] Due to these limitations, several additions to the modified Duke criteria have been proposed to increase its sensitivity. First, serologic evidence of active infection with *Coxiella burnetii* has been added as major criterion (but results are relatively late). Second, although modern diagnostic options (e.g. molecular detection of pathogens in relevant specimens such as vegetations) are not formally part of the modified Duke criteria (yet), detection by these methods are usually counted clinically as major criterion provided that the identified species is clinically plausible. Also, automated systems have increased both sensitivity and speed of blood cultures (large reduction in “culture-negative” cases), as well as their specificity to a certain extent (if time to positivity is taken into account).

Major criteria
1. Blood cultures positive for IE a. Typical microorganisms consistent with IE from 2 separate blood cultures: • Viridans streptococci, *Streptococcus gallolyticus* (*Streptococcus bovis*), HACEK group, *Staphylococcus aureus*; or • Community-acquired enterococci, in the absence of a primary focus; or b. Microorganisms consistent with IE from persistently positive blood cultures: • ≥2 positive blood cultures of blood samples drawn >12 h apart; or • All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or c. Single positive blood culture for *Coxiella burneti* or phase I IgG antibody titre >1:800.
2. Imaging positive for IE a. Echocardiogram positive for IE: • Vegetation; • Abscess, pseudoaneurysm, intracardiac fistula; • Valvular perforation or aneurysm; • New partial dehiscence of prosthetic valve. b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT. c. Definite paravalvular lesions by cardiac CT
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use. 2. Fever defined as temperature >38°C. 3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway's lesions. 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor. 5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Table 4: Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis.[12] CT = computed tomography; FDG = fluorodeoxyglucose; HACEK = *Haemophilus parainfluenzae, H. aphrophilus* and *H. paraphrophilus* (currently referred to as *Aggregatibacter aphrophilus* and *A.paraphrophilus*), *H. influenzae, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*, and *Kingella denitrificans*; IE = infective endocarditis; Ig = immunoglobulin; PET = positron emission tomography; SPECT = single photon emission computerized tomography. Adapted from the modified Duke criteria by Li *et al*.[39]

The list of minor criteria is more extensive and includes predisposing heart conditions, drug use by intravenous injection, presence of fever, vascular phenomena, immunologic phenomena, and microbiological evidence that not meet major criteria (positive blood cultures or serology). The rationale for their inclusion depends on the specific criterion. For example, as fever is present in around 90% of endocarditis patients[16], its absence makes this diagnosis less likely (at the same time realizing that this sign is nonspecific).[38] In addition, major arterial emboli provide supporting evidence for the presence of an infected intravascular lesion and, therefore, also for endocarditis (including septic pulmonary emboli in right-sided endocarditis).[38] Mycotic aneurysms, although much less common than emboli, are also strongly associated with endocarditis, implying the presence of this disease.[38] Central nervous system hemorrhages can result from either septic emboli or mycotic aneurysms, which are both associated with endocarditis.[38] Elevated levels of rheumatoid factor that resolve with treatment have been reported in 30-50% of cases of subacute and in 25% of cases of acute endocarditis,[38] thus directing diagnosis towards endocarditis if high levels are measured without a plausible alternative explanation. However, pre-existing positive rheumatoid factor cannot be counted as minor criterion.[38] Immune complex glomerulonephritis, although uncommon, is an important complication of endocarditis, and, therefore, the presence of >40% microscopically observed dysmorphic erythrocytes count as another minor criterion.[38] Finally, because it is of lower predictable value, a bacteremia that is neither typical nor

persistent counts as minor criterion. Of note, serologic evidence of active infection with microorganisms consistent with rare forms of endocarditis count as minor criterion as well.

Clearly, many of the minor criteria are of variable value as they largely depend on the quality of the history taking and physical examination. Furthermore, there is often debate in clinical practice about which cardiac conditions to appoint as predisposing for endocarditis and which not. This classification seems to be largely dependent on time, changing with the common paradigm about which cardiac conditions are at highest risk of infective endocarditis and thus should be considered for antibiotic prophylaxis during high-risk procedures.[12,38,50] The most recent European guideline restricts the patients considered as predisposed to the three groups mentioned before (see "prophylaxis").[12] At the University Medical Center Groningen (UMCG), we additionally regard the presence of a pacemaker or ICD as predisposing heart condition. In theory, almost any type of structural heart disease may predispose to endocarditis, especially if the defect results in turbulence of blood flow.[15]

Imaging

Echocardiography is historically considered the designated modality to provide imaging evidence of endocarditis. Therefore, it has been regarded as a major criterion in the modified Duke criteria, as previously described. In light of the limitations of echocardiography, recent international guidelines aim to increase the diagnostic accuracy for infective endocarditis, intracardiac prosthetic material related infection and their extracardiac sequelae by inclusion of additional imaging modalities.[12,13] However, many uncertainties remain, as shown by the large differences in the way that these imaging modalities were implemented in the recent European[12] and American[13] guidelines. Additional imaging is advised to be performed in individual patients in the European guideline, but is only mentioned as potential diagnostic possibility in the American guideline.[12,13] Retrospectively, ECG-gated multidetector computed tomography angiography (MDCTA), retrospectively ECG-gated magnetic resonance imaging with angiography (MRA), ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) including low-dose CT (FDG-PET/CT), and leukocyte scintigraphy have been evaluated in this regard.

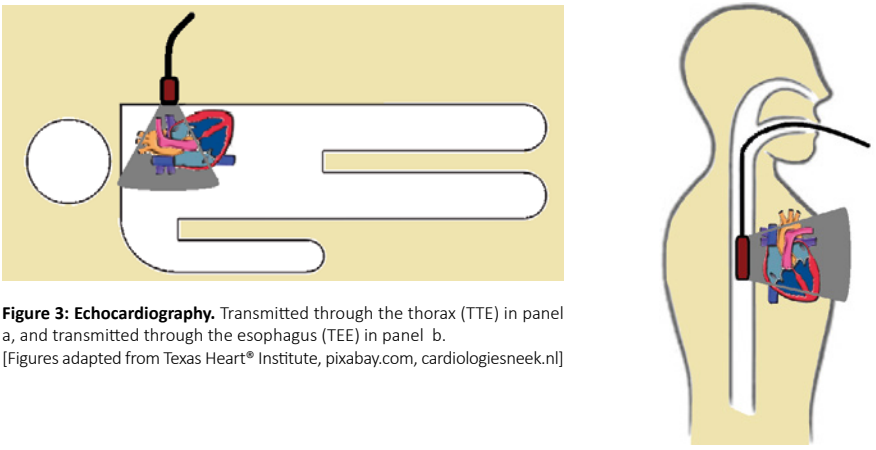

Figure 3: Echocardiography. Transmitted through the thorax (TTE) in panel a, and transmitted through the esophagus (TEE) in panel b.
[Figures adapted from Texas Heart® Institute, pixabay.com, cardiologiesneek.nl]

Echocardiography

Echocardiography is an imaging technique using high frequency sound waves (ultrasound) and their echo to create images, either transmitted through the thorax (TTE) or the esophagus (TEE) (Figure 3). New developments include 3-dimensional (D) echocardiography, clinically used by some due to the development of high-quality real-time TEE.[51] TEE has risks such as ulcus formation or even perforation by the probe and problems swallowing, breathing, nausea and hypotension by the topical anesthetic medication used to numb the throat (lidocaine) or to sedate the patient (e.g. midazolam, propofol).

Retrospectively ECG-gated MDCTA

CT angiography is an anatomical imaging technique using computer algorithms to combine many X-rays taken from different angles to produce cross-sectional (tomographic) images of scanned blood vessels and organs, after infusion of a contrast agent (Figure 4). As the heart beats continuously, creating blurry images, ECG-gating is used to group the images according to the cardiac phase, to improve image quality, and thereby increase diagnostic accuracy for endocarditis. Technically this means that a minimum requirement for the spatial resolution is a ≥64 detector scanner. Furthermore, in contrast to routine practice where 10-phase datasets (at 10% increments through the cardiac cycle) are reconstructed, reconstruction of 20- or 25-phase datasets (at 5% or 4% increments of the R-R interval) is required to depict valve motion and valvular pathology, such as hypermobile vegetations. Retrospective ECG-gating means that this cardiac cycle-based reconstruction takes place after gathering non-gated data for the whole cardiac cycle. Side-effects of MDCTA scanning are the detrimental effects of ionizing radiation, such as an increase of the risk of cancer.

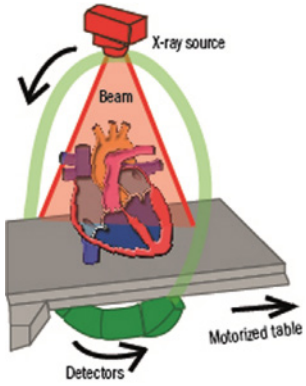

Figure 4: Multidetector computed tomography. Subject on motorized tables moves forward, while X-ray source circles around the organs of interest and beam of X-rays are projected on detectors on opposite site of circular source-trajectory. [Figure adapted from Texas Heart® Institute and FDA.gov, with many thanks to Maaike van Dijk]

Retrospectively ECG-gated MRA

MR angiography scanning is an imaging technique that uses strong magnetic fields to align atoms and measures electromagnetic fields emitted at relaxation of the atoms to generate anatomical images of scanned blood vessels and organs, after infusion of a contrast agent. In addition, this technique can also provide functional data, for example on jets and metabolism. It uses hydrogen atoms which absorb and emit radio frequency energy when placed in a magnetic field, so no ionizing radiation is involved. As

hydrogen atoms are particularly abundant in water and fat, MRI is especially good in mapping water and fat in the body. Computer algorithms generate cross-sectional images from the emitted radio waves. Again, retrospective ECG-gating is required to group the images according to the cardiac phase, in order to improve image quality and thereby increase diagnostic accuracy for endocarditis. Another technical requirement is a minimum of 1.5 Tesla for a spatial resolution enabling cardiac and thus endocarditis assessment. Unfortunately, certain non-removable metal inside the body such as some pacemaker/ICDs are a contra-indication to perform a MRI scan.

FDG PET/CT

FDG-PET/CT is a functional imaging technique using radiolabeled glucose (^{18}F-FDG) that is nonspecifically taken up by active cells, such as malignant cells (in cancer), macrophages and monocytes (in inflammation), and activated granulocytes, lymphocytes and bacteria (in infection).[53] FDG is transported across the cellular membrane by the integral membrane GLUT1-proteins, whereafter intracellular FDG is phosphorylated and trapped inside the cell.[53] ^{18}F-FDG is suitable for imaging 60 minutes after injection and ^{18}F undergoes positron emission decay which is used for imaging (physical half-life of ^{18}F is 110 minutes and the biological half-life of FDG is similar). The positrons collide with electrons creating two gamma photons traveling in opposite directions, and these are detected by the camera system (Figure 5). A low dose CT-scan accompanies the PET-scan to provide a map where the positrons (or two photons) originated from the body. A FDG-PET/CT scan is usually performed from the skull to mid-thigh (or sometimes from top to toe), enabling identification of the portal of entry and detection of extracardiac infectious manifestations of endocarditis in addition to the visualization of an active cardiac infectious process.[54] Side-effects of FDG injection are uncommon. The only side-effect of note is the ionizing radiation of both the PET and the low-dose CT scan.

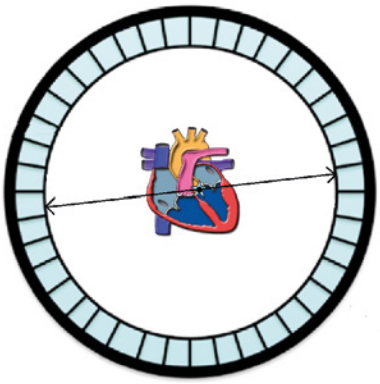

Figure 5: Positron emission tomography. After positron emission decay of radiolabeled glucose (^{18}F-FDG), the positron travels a short distance and collides with an electron to create two γ-photons that travel in directions 180° from each other. These photons that are detected in pairs of two are consequently analyzed to create the image.
[Figure adapted from Texas Heart® Institute and physicsforums.com]

Leukocyte scintigraphy

Leukocyte scintigraphy is a functional imaging technique using radiolabeled leukocytes. After planar/static imaging and identification of the site of infection, single-photon emission computed tomography (SPECT) with a low-dose CT can be performed to obtain tomographic images with adequate spatial resolution for an exact localization. SPECT measures the gamma photons emitted from the injected

radiotracer, creating plane 2D images from multiple angels which are subsequently reconstructed in 3D images by a computer algorithm.[52] A low dose CT scan accompanies the SPECT-scan to provide a map where the photons originated from the body. Important in leukocyte scintigraphy is to obtain multiple images over time to be able to distinct infection from inflammation.[53]

There are different techniques to radiolabel leukocytes in order to image their anatomical accumulation. First, leukocytes can be isolated from the patients' blood and radioactively labeled *in vitro*. The labeled compounds enter viable leukocytes which are hereafter re-injected into the patient. Second, radioactively labeled monoclonal antibodies (or fragments) targeting leukocyte-specific surface markers can be injected in order to visualize sites of leukocyte accumulation *in vivo*. *In vitro* labeling of leukocytes is mostly used in the detection of endocarditis, with either Technetium-99m (^{99m}Tc) or Indium-111 (^{111}In).[52]

Identification of microorganisms

In addition to microbiological diagnostic testing in infective endocarditis by blood cultures (providing clinical Duke criteria), have culturing and molecular testing on explanted heart valves directly been performed if patients undergo cardiothoracic surgery during the active phase of infection (providing pathological Duke criteria). To increase the availability and reliability of the obtained microbiological evidence in endocarditis, new techniques can be considered such as sonication of explanted heart valves in these patients, as addition to the standard diagnostic work-up of endocarditis. Sonication is a method using ultrasonic waves to mobilize bacteria from the biofilm on the surface of explanted (prosthetic) material.[23,46-48,55] Mechanical vibration by the ultrasonic waves causes microscopically small air bubbles in the fluid in which this explanted material is placed for the procedure. The energy released with the implosion of these air bubbles causes local micro voltages, shear forces and oscillating cavitation bubbles, which destroy the biofilm on the surface. Fortunately, cell structures are not significantly damaged during this process and microorganisms can still be cultured and molecularly identified from the fluid. Indeed, studies have shown an improvement of microbiological results after addition of sonication to the standard diagnostic workup for orthopedic prosthesis infections, as well as for pacemaker/ICD infections.

Therapy

Not only diagnosing infective endocarditis causes clinical dilemmas, but also the choice of therapy often causes discussions among the treating physicians. The two mainstays of treatment are early and appropriate antimicrobial therapy and cardiothoracic surgery, the last one often in combination with source control of remote foci. Optimal treatment of patients with endocarditis remains difficult, since there are many uncertainties and the disease and therapies caries high risks of complications for the patient.

Antimicrobial therapy

Antimicrobial therapy in infective endocarditis consists of high-dose and long-term intravenous

antibiotics for bacteria and antimycotic drugs for fungi/yeasts. Depending on the individual situation of the patient (epidemiology, risk factors, geographical area), an empiric regimen is started until a pathogen is identified, after which a specific and targeted regimen is chosen. To increase the therapeutic efficacy of antibiotics in infective endocarditis, optimization of dosing regimens of commonly prescribed antibiotic agents should be considered. For example, guidelines recommend the use of an aminoglycoside (e.g. gentamicin), combined with beta-lactams (e.g. penicillins or cefalosporins), for antimicrobial treatment of endocarditis for some, mainly gram-positive, pathogens.[11,12] In clinical practice the main indication for gentamicin is prosthetic material-related infection, but also native infections with streptococci to shorten the total duration of antibiotic treatment by its addition for two weeks if complicating factors are absent, and enterococci.

Aminoglycosides, most commonly used is gentamicin, are small, hydrophilic molecules with a volume of distribution (Vd) that is similar to the extracellular fluid (all bodily fluid outside of the cells, thus equal to blood plus interstitial fluid).[56] Their clearance from the human body is proportional to the kidney function (glomerular filtration rate).[57] Aminoglycosides bind to the bacterial cell membrane and undergo active transport into the cytosol to reach their site of action.[15] Their main site of action is the bacterial ribosome, the organel responsible for protein synthesis. As aminoglycosides interrupt this process, they are classified as bactericidal. It is assumed that cell wall-active antibiotic agents, such as beta-lactams, increase the access of gentamicin to the bacterial cell membrane, especially in gram-positive micro-organisms. In this way, a synergistic bactericidal effect between a cell wall-active antibiotic and gentamicin is achieved.[58] Therefore, gentamicin is effective in lower concentrations in the treatment of endocarditis, as compared with other indications.[59] Furthermore, the synergistic action enables a shorter duration of the total antibiotic therapy in some cases.[60]

Therapeutic efficacy of gentamicin in endocarditis depends on obtained serum levels. In itself, obtained gentamicin serum levels are determined by both pharmacokinetic (PK) and pharmacodynamic (PD) parameters. Pharmacokinetic parameters describe the chemical metabolism of gentamicin within the patient, depending for example on the volume of distribution and renal clearance. Conversely, pharmacodynamic parameters describe the biochemical and physiologic effects of gentamicin on the patient, depending for example on bactericidal effect and toxic potential. Because of the intra and inter individual differences in these parameters, variable dosing of gentamicin is recommended for optimal eradication of endocarditis and survival of patients.

Cardiothoracic surgery

Cardiothoracic surgery in infective endocarditis involves the resection of the infectious process as well as the restoration of heart (valve) function by correction of any cardiac anatomical alterations, such as vegetations, abscesses, fistula, shrunken valves, valve tears or defects, and prosthetic valve detachment. 25-50% of patients are operated during the acute phase of infection and an additional 20-40% afterwards due to hemodynamic complications.[8] Furthermore, early surgical intervention improves outcome compared with medical therapy alone, reducing 6 month mortality from 33% to 16% patients

with complex endocarditis.[61] However, extensive derangements due to endocarditis can be technically difficult to repair. To increase the therapeutic efficacy of cardiothoracic surgery in endocarditis, it is important to optimize the techniques and prostheses used.

After destruction of a heart valve by endocarditis, a valvular plasty or even replacement of a valve can be needed. Moreover, if there is more perivalvular damage, extensive surgery and replacement of more cardiac parts might be needed. As the aortic valve is the most often affected valve in infective endocarditis, this is an important therapeutic target for optimization. Historically, cryopreserved homografts were the gold standard in patients with extensive aortic valve endocarditis.[62-64] Nowadays, biological stentless valves are more often used.[65,66] A cryopreserved homograft is an aortic valve (with aortic root) taken from a human donor. Conversely, a stentless bioprostheses consists of a stentless porcine aortic root prosthesis.

Interdisciplinary research group at the UMCG

With the ultimate aim of improving diagnosis and outcome in patients with infective endocarditis, a research team was set up in the UMCG. Because of the many different aspects of this disease, we reasoned that a multidisciplinary approach, also with regard to research, is the key to improve outcome. Therefore, a multidisciplinary study group of representatives from cooperating medical departments was formed, including Medical Microbiology (Anna Gomes, Bhanu Sinha), Infectious Diseases (Sander van Assen, Kasper Wilting), Cardiology (Peter Paul van Geel, Joost van Melle, Alexander Maass), Thoracic Surgery (Ehsan Natour), Nuclear Medicine and Molecular Imaging (Riemer Slart, Andor Glaudemans, Ronald Borra), Radiology (Tineke Willems, Niek Prakken), and Clinical Pharmacy and Pharmacology (Daan Touw). Furthermore, in order to truly improve outcome of patients with endocarditis, we investigated several chain links of the in-hospital process of care for these patients. Optimal application of diagnostic modalities helps to establish a definite diagnosis, which subsequently allows for better risk stratification for therapy. Therefore, we aimed to optimize the diagnostic workup as well as the available therapeutic options. To our opinion, only if all parts of the chain are strong enough, the patient will substantially benefit, i.e. a better outcome.

Figure 6: Logo of our study IDENTICAL.

Improving **D**iagnosis of **EN**docarditis and its **T**herapy with a focus on prosthet**IC** materi**AL** was our focus,

and therefore we decided to use the umbrella-term "**IDENTICAL**" (Figure 6). IDENTICAL now consists of retrospective studies, a prospective single center study, and several collaborations with colleagues in the field of endocarditis from other centers. A stronger total chain of care should translate into increased length and quality of life for patients and reduced costs for healthcare, both for patients with endocarditis and for patients with an alternative diagnosis. In light of increasing healthcare costs and with the sustainable aim to optimize patient care, we are confident that IDENTICAL leads to a more (cost) efficient use of diagnostic modalities, and contributes to an individualized and improved therapy.

Outline of this thesis

This thesis aims at providing opportunities for improvement of care for patients with suspicion of infective endocarditis, by optimization of several chain links of the in-hospital process of care. This thesis consists of three parts. In the first part (Chapters 2 to 7) several aspects for improving the diagnostic workup of patients suspected of infective endocarditis are discussed. **Chapter 2** shows a systematic literature review that we performed on the diagnostic value of other imaging techniques in addition to echocardiography for infective endocarditis, with a proposal of an updated diagnostic workup. In **Chapter 3** we subsequently evaluated the proposed flowchart after its implementation in the clinical protocol for endocarditis in our hospital, the UMCG, the Netherlands. We performed a head-to-head comparison of echocardiography and the newly introduced techniques FDG-PET/CT and MDCTA. Also, we provide data regarding specific strengths and weaknesses of the different techniques. In **Chapter 4** we investigated possibilities to improve the diagnostic performance of FDG-PET/CT in prosthetic valve endocarditis. We used both visual and standardized quantitative assessments in a large multicenter cohort, comprising patients suspected of prosthetic valve endocarditis and absolute negative controls. In **Chapter 5** we conveyed a clear message concerning the role that FDG-PET/CT should have in the diagnostic workup of infective endocarditis and related intracardiac prosthetic material. Furthermore, in **Chapter 6** we propagate that the next step after performing a FDG-PET/CT scan in the diagnostic workup of infective endocarditis, is to use the provided information in the therapeutic planning for an individual patient. In addition to the optimization of the imaging link to diagnose endocarditis, we investigated the optimization of the microbiological link to diagnose endocarditis in **Chapter 7**. In this chapter, we investigated the value of sonication of explanted heart valves for the microbiological diagnosis of patients with infectious endocarditis undergoing cardiothoracic surgery, in addition to the standard workup.

The second part of this thesis (Chapters 8 and 9) deals with aspects for optimizing therapy for patients with infective endocarditis. In order to improve the antimicrobial therapy of infective endocarditis patients, we developed a pharmacokinetic model of gentamicin specifically for this patient group, which is explained in **Chapter 8**. After the development of this specific endocarditis gentamicin model, we validated this new model together with the two already existing models for patients admitted to the intensive care unit and patients admitted to a general hospital ward, respectively, in our second cohort of patients. Furthermore, in order to improve the surgical therapy, we provide evidence for the opportunity to safely treat patients with aortic valve endocarditis complicated by paravalvular abscess

formation during cardiothoracic surgery with a stentless bioprosthesis in **Chapter 9**. Its use is illustrated with high-quality intraoperative macroscopic pictures, in addition to echocardiographic, radiological, and nuclear imaging from these patients.

Lastly, in the third part of this thesis (Chapters 10 to 12), directions for future development, which could further improve care for patients suspected of endocarditis, are discussed. In **Chapter 10** we argue for the improvement of care for patients with (suspected) infective endocarditis by the implementation of regular meetings in a multidisciplinary Endocarditis Team. In this chapter, our experiences with the setting up of this team are shared and advice is given on how to tackle potentially encountered problems. In **Chapter 11** we reveal a glimpse about preclinical studies and future opportunities in clinical applications of more specific, bacteria-targeted imaging in several different infectious diseases, including infective endocarditis. And in **Chapter 12** we provide a general discussion to put all results from this thesis into the perspective of daily clinical practice, as well as to bundle the most important learning points that need special emphasis. Furthermore, in this chapter an impression is given about the effects of the research covered in this thesis on daily clinical practice. Finally, suggestions for directions of future research are discussed.

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