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The Endocarditis Team

English translation, based on Dutch release in Nederlands tijdschrift voor Medische Microbiologie (=Dutch Journal of Medical Microbiology).



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Summary

Endocarditis is a life-threatening disease with high mortality and morbidity. In clinical practice, we try to improve the outcome of patients with endocarditis by implementing a better and faster diagnostic workup, a timely start of antimicrobial therapy and an early surgical intervention if required. In the most recent update of the guidelines for the management of patients with endocarditis, an Endocarditis Team is put forward as crucial part in the improvement of care for patients with (suspected) endocarditis. They state that endocarditis requires a multidisciplinary approach since patients present with highly variable signs and symptoms, need a high-standard of care from several medical specialists, and need to be discussed in a surgical team early in the course of the disease. Observational studies support this implementation by showing a marked decrease in mortality after discussing endocarditis patients in an Endocarditis Team. This article discusses the experience with the implementation of an Endocarditis Team in two different regions of the Netherlands (Rotterdam-Rijnmond and Groningen). Which aspects are important for the structure and function of an Endocarditis Team? Setting up of an Endocarditis Team can be difficult, therefore we provide some practical advice. Finally, an illustrative case is presented.

Introduction

Endocarditis is a severe disease with high mortality and morbidity. Published mortality rates are in the in-hospital and active phase of disease 14-22% and 40% after one year (even 25-59% for prosthetic valve endocarditis).^{1,2} The high morbidity results from local cardiac destruction and bodily infarcts due to embolism formation. The incidence of endocarditis did not decline as a result of a change in risk factors.³ In countries with high incomes, the risk factors of degenerative heart disease, congenital heart disease, intravenous drug use, diabetes mellitus, cancer and heart failure became more common; intracardiac prosthetic material is also implanted more often (prosthetic valve, pacemaker/implantable cardioverter defibrillator, patches) and the population aged.^{2,3} In clinical practice, we try to improve the care for these patients through prompt and adequate diagnosing and early start with adequate antimicrobial therapy combined with surgical therapy if indicated. Therefore, it is essential to identify the pathogen and its antimicrobial resistance pattern if possible, including the minimum inhibitory concentration (MIC) of the pathogen for different antibiotic agents.

For the diagnosis of infective endocarditis, important support is provided by the modified Duke criteria⁴, supplemented with the guidelines of the European Society of Cardiology (ESC)⁵ and the American Heart Association (AHA).^{6,7} In these recent guidelines a number of critical adaptations are introduced. For the first time “the Endocarditis Team” is presented as critical part in the care for patients with (a suspicion of) endocarditis.⁵⁻⁸ In addition, a prominent place is given to non-invasive imaging techniques as addition to echocardiography, namely F-18 fluorodeoxyglucose positron emission tomography with low-dose computed tomography (FDG-PET/CT), cardiac CT, and single-photon emission computed tomography (SPECT)/CT with radiolabeled leukocytes.⁵

The Endocarditis Team

The European guidelines on endocarditis (ESC)⁵ state that endocarditis should be managed by a multidisciplinary team as: 1) it is a complex disease, presenting with highly variable signs and symptoms depending on the first involved organs, the underlying heart disease, the pathogen, the resulting complications and the characteristics of the patient; 2) expertise is needed from several medical specialties (including cardiology, cardiothoracic surgery, internal medicine/infectious diseases, medical microbiology); 3) an important proportion of patients has an indication to undergo surgery during hospital admission and therefore it is important to discuss patients early in their course of disease in a surgical team.⁹

For a true clinical impact of an Endocarditis Team, it is important to critically evaluate all clinical and diagnostic data during a meeting with all medical specialists present in order to develop and evaluate an individual plan for each patient. The modified Duke criteria provide a basic structure to come to a diagnosis of endocarditis (sensitivity and specificity of approximately 80% for native valves⁴ and an even lower sensitivity and specificity in case of missing information and/or intracardiac prosthetic material *in*

situ). However, clinical reasoning by experts in the individual context of the patient is critical to come to the final diagnosis.² A point of caution is the way that missing information is handled in this regard (for example diagnostic tests that are not at all or not completely available, e.g. one set of blood cultures before starting antimicrobial therapy, only).

Two European observational studies indeed showed that the outcome of patients with endocarditis is improved after discussing them in an Endocarditis Team. A French observational study included 333 patients with definite endocarditis according to the modified Duke criteria, including streptococci, enterococci, staphylococci and micro-organisms of the HACEK-group as pathogens.¹⁰ A significant reduction from 18.5% to 8.2% was reported in the one-year mortality after introduction of a multidisciplinary Endocarditis Team.¹⁰ An Italian observational study included 292 patients with definite native valve endocarditis according to the modified Duke criteria.¹¹ In this study, a formalized, multidisciplinary and coordinated workup was introduced stating that patients needed to be evaluated within 12 hours after hospital admission, early surgery of patients with an indication (within 48 hours if needed) and weekly evaluation of stable patients. A significant reduction was reported of in-hospital mortality (from 28% to 13%), of surgery-related mortality during the active phase of disease (from 47% to 13%), and of three-year mortality (from 34% to 16%). Based on these two studies, the American guideline for the management of patients with valve disease (AHA/ACC) recommended to have an Endocarditis Team in reference centers (class IB).⁷

Setting up an Endocarditis Team in your center

The Endocarditis Team should operate in consultation with all regional medical specialties involved in the care for patients with infective endocarditis. This type of specialized patient care should ultimately be centralized in order to increase the required experience and expertise. This centralization can physically be best situated in an academic hospital or top clinical center concerning logistical reasons. It is advised to set up “satellite Endocarditis Team” in all referring centers, as to optimize the diagnostic workup and therapy as early as possible and before the planned care is discussed with the Endocarditis Team in the referral center.

Where to start with the setting up of an Endocarditis Team? The European guideline⁵ provides some support by giving answers for questions such as: 1) When to refer a patient with endocarditis to the Endocarditis Team in a referral center? 2) Which expertise is demanded in a referral center? 3) Which composition and role should an Endocarditis Team have? This article discusses these three questions in the guideline⁵ (originally in Dutch), supported by providing our concept of, and experience with, setting up of an Endocarditis Team in our regions. Which aspects are important for the structure and function of an Endocarditis Team? We experienced that setting up of an Endocarditis Team can be difficult. Therefore, we provide some additional practical tips. At the end of this article, we describe an illustrative case (Figure 2a) to highlight the function and added value of the Endocarditis Team.

The structure and function of an Endocarditis Team

Tasks of the Endocarditis Team⁵

- Central role in diagnostics and therapy for patients with (a suspicion of) endocarditis, including bed-side consultation by an internist/infectious disease (ID) specialist, antimicrobial/diagnostic stewardship, referral and follow-up.
- Improvement of the quality of medical care for patients with endocarditis (cycle for quality improvement).
- Participation in local, national and international patient registries, with publication of mortality and morbidity in the medical center.
- Patient education programs.

Characteristics of a referral center⁵

- Easy access to cardiothoracic surgery.
- Direct access to diagnostics: transthoracic (TTE) and transesophageal (TEE) echocardiography, diagnostic CT for the heart, MRI and nuclear imaging (¹⁸F-FDG PET/CT, possibly SPECT/CT with radiolabeled leukocytes).
- Endocarditis Team is physically present.

Composition of an Endocarditis Team⁵

Several medical specialties form the core of the team. This core team can be expanded if needed:

- Core team: cardiologists with expertise in echocardiography and valvular heart disease, cardiothoracic surgeons with expertise in the field of valve surgery and endocarditis, internist/ID specialists, medical microbiologists, radiologists and nuclear physicians with specific expertise in the field of endocarditis.
- Expansion, indicated per patient: cardiologists with expertise in pacemakers / implantable cardioverter defibrillators or congenital heart disease, intervention cardiologists, neurologists, orthopedics, hospital pharmacists with expertise in the field of drug level measurements / therapeutic drug monitoring (TDM) and the application of pharmacokinetics / pharmacodynamics (PK/PD), vascular surgeons, intensivists.

Selection of patients

- The selection of patients should take place daily, as to assess the urgency for the medical care needed. This selection can be carried out by all members of the Endocarditis Team. If necessary, members should be able to consult each other easily, for example in the daily heart team discussion.
- Discussion by the Endocarditis Team:
 - o Any patient with (a reasonable suspicion of) endocarditis, including patients with *Staphylococcus aureus* bacteremia, can be signed up for discussion in the Endocarditis Team. Even in patients with a 'straight forward' clinical picture, a

discussion in the multidisciplinary team can have clear benefits. Therefore, it is advisable for referral centers to have a low threshold for signing up and discussing their patients in the regional Endocarditis Team, especially in the beginning after its setup, so that its procedures become well-known.

- For patients with uncomplicated endocarditis, regular consultation with the Endocarditis Team is recommended, with consultation and external visitation in the referral center if necessary (class IIa, level B). The intensity of this contact depends on the clinical condition of the patient and the available and required diagnostic and therapeutic expertise of the referring center.
- Transfer to the reference center:
 - Complicated endocarditis: heart failure (hemodynamic instability or decompensation), abscess formation (or cavitation in other ways, e.g. mycotic aneurysm), neurological or otherwise embolic complications.
 - Indication for surgical therapy: heart failure, uncontrolled infection, prevention of embolism. A distinction is made between emergency (within 24 hours), urgency (within 24-72 hours), and elective surgery. In the discussion whether or not to perform a surgical procedure (and when), the cardiothoracic surgeon's judgment is important but evaluating a patient's operability by the cardiologist and intensivist is also crucial.
 - (Suspicion of) prosthetic valve endocarditis, because these patients are at high risk for complications (including valve dehiscence) and often require additional diagnostics (with advanced scanners), complicated antibiotic treatment and possibly an (acute) reoperation (with high mortality rates).
 - Consider, in case of (suspicion of) device or lead infections, recurrent endocarditis, congenital heart disease or extensive comorbidity that can complicate treatment or further diagnostics.

Meetings by the Endocarditis Team

- Purpose: to provide recommendations on referral, additional diagnostics, surgery, antimicrobial therapy (drug, dosage and dosing schedule, duration), and follow-up.
- Frequency: we believe that the Endocarditis Team should preferably meet at regular intervals and at least once a week, depending on the number of patients signed up. However, in the first phase after the implementation of the team, meetings on an ad hoc basis may be more appropriate, depending on the number of signed up patients.
- Organization: meetings can be structured based on a predefined protocol (see Figure 1).
- Coordination: it is important that one central person (e.g. a PhD student, resident, or medical specialist, with a pre-defined back-up person if needed) is responsible for the preparation of a meeting, possibly carried out by a secretariat. This coordinator of the team should organize the whole meeting.

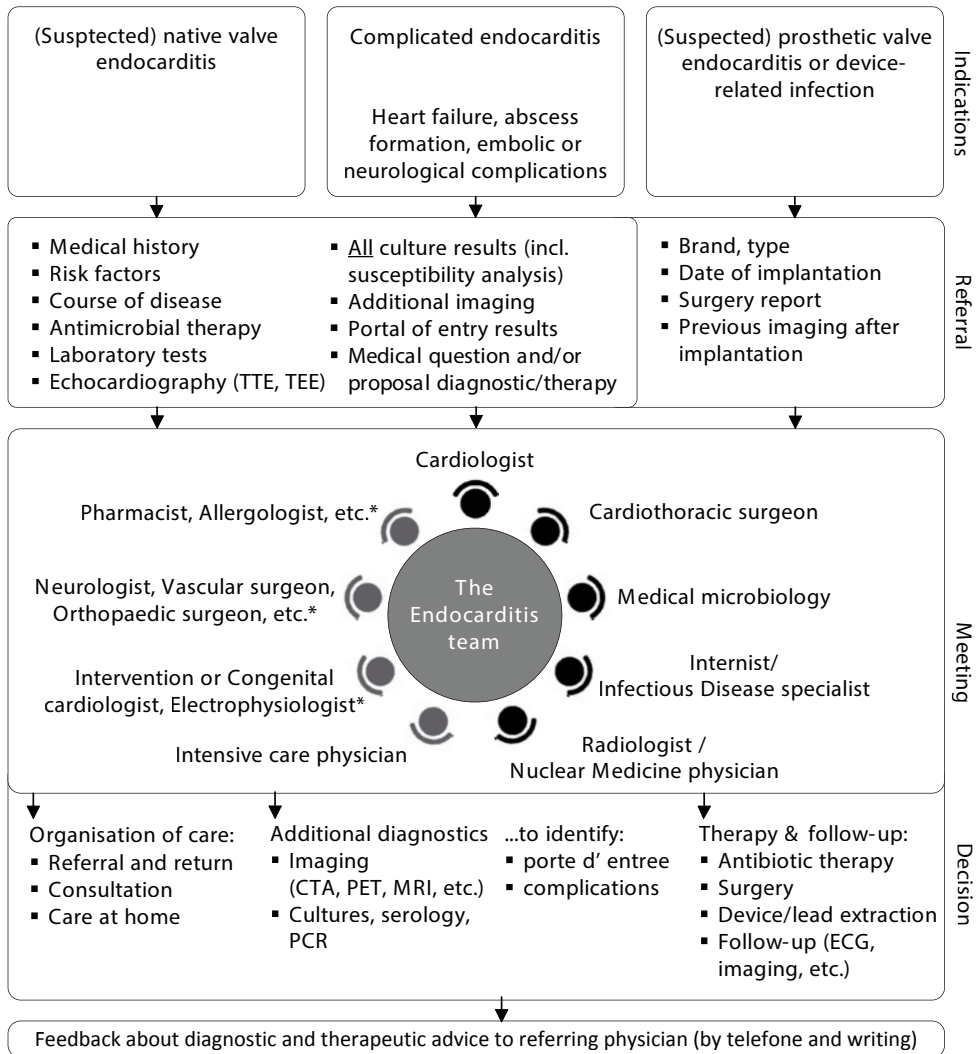


Figure 1: Structure and procedures of the Endocarditis Team. Discussions should be structured based on a pre-established protocol.

Note: advice on the antimicrobial treatment concerns the choice of the right agents, dose and dosing schedule, the duration and follow up (measurement of blood levels/TDM and resulting adjustments) and PK/PD assessment based on MIC determination to ensure optimal effectiveness and minimal toxicity.

* Additional specialisms, present on indication.

- Registration: patients can be signed up via a standardized registration form (input). Clear requirements should be defined about the minimum patient data needed for discussion in the Endocarditis Team.
- Recommendation: a meeting by the Endocarditis Team should result in a joint recommendation concerning diagnostics, therapy and follow-up for the patient discussed (output). Reporting

of this recommendation ideally takes place by a letter or in the electronic patient file.

- Follow-up: during clinical admission and at the outpatient clinic after hospital discharge, with an individualized and clinically controlled frequency (ideally 1, 3, 6, and 12 months). Imaging is planned if indicated, for example in case of prosthetic valve endocarditis after the antimicrobial therapy or after heart valve surgery to obtain a baseline of the new anatomical situation.

Practical tips for setting up an Endocarditis Team.

1. Where to start?

If your center can act as a referral center, we recommend: 1) to develop an endocarditis protocol / guideline for your own referral center to communicate your workup and addresses for consultation. This can subsequently be shared with referring centers in the region; 2) to develop a joint scan protocol for diagnostic CT imaging of the heart and FDG-PET/CT imaging of the whole body after proper patient preparation, facilitating adequate imaging by means of a “one-stop shopping” principle.

Next, it is useful for setting up of an Endocarditis Team to appoint two dedicated endocarditis experts per medical specialty as members of the core team. Of such a couple, at least one should be present during team meetings and the other should be available as back-up.

If the Endocarditis Team has been set up, we would recommend to inform the medical specialists involved (including cardiologists, cardiothoracic surgeons, internist/ID specialist, medical microbiologist) in the possible referral centers in the region, to explain the role and purpose of your team.

2. Find a moment for regular meetings

It is recommended to build further on logistics already present. The regular heart team meetings (present: cardiologist, cardiothoracic surgeon), which will be present daily in most reference centers, seems to be the most appropriate moment to exploit for this purpose. As next step, it is important to invite an internist/ID specialist, medical-microbiologist, radiologist, and nuclear medicine physician to this meeting. In January 2016, a start was made with the setting up of an Endocarditis Team at the Erasmus Medical Center (EMC). It proved to be relatively easy to additionally invite the medical microbiologist, internist/ID specialist, radiologist and nuclear medicine physician to discuss patients with (suspected) endocarditis in the heart team meetings. It was only six months later that the Endocarditis Team meetings were permanently scheduled on a regular basis, on average resulting in 2-3 patients to discuss each week. At this time, the number of patients signed up from the region had increased as a result of a lower perceived threshold for consultation within the region. Once again, existing logistics were used: every Tuesday and Thursday a multidisciplinary meeting was already scheduled in which a cardiologist, cardiothoracic surgeon and an internist/ID specialist or a medical-microbiologist were present. By organizing the Endocarditis Team meetings directly after this already existent multidisciplinary meeting, only the imaging specialists needed to be additionally invited.

As a back-up, we would recommend to agree on how to meet on an ad-hoc basis in the Endocarditis Team in case patients are to be discussed but cannot wait until the next regular meeting. At the EMC, cardiologists and cardiothoracic surgeons have agreed that the physicians who consult the intensive care that day will join the meeting. In addition, the medical microbiologists and internists/ID specialists agreed that the consulting medical microbiologist or internist/ID specialist of that day will also join.

3. Where can patients be registered for discussion in the Endocarditis Team?

We recommend that patients are registered for discussion in the Endocarditis Team via an already involved secretary, for example the secretary of the Department of Thoracic Surgery (where patients are also registered for discussion in the regular heart team). Thereafter, this secretary can inform the Endocarditis Team via a special e-mail address, from where the coordinator can actively invite the other team members to a meeting. With this invitation, all relevant data from the patients to be discussed during the meeting, including referral letters, can be attached, so that all attending members can prepare themselves and additional data can be tracked down if needed (for example the antibiogram and MIC values for antibiotics of a pathogen cultured in another center).

A joint e-mail address was created in the EMC to which all members of the Endocarditis Team have access. Via this joint e-mail address internal consultation can take place about questions from referring physicians and a joint answer can be formulated.

It is important to clearly communicate the logistics concerning the registration of patients and the feedback from the discussed patients during the meeting to the referring physicians, for example in a newsletter. A short pocket manual or a website are also convenient means for this purpose.

4. Which data should at a minimum be provided during patient registration?

Concerning minimally requested diagnostic data, referring physicians should in our opinion at least provide a good echocardiography (images, not only the reports, and preferably also TEE) for their patients to be discussed in an Endocarditis Team meeting. In addition, the results of all blood cultures should be provided, including information regarding the use of antimicrobials at the time of blood culture collection, incubation duration,¹² susceptibility spectrum and MIC values if applicable and/or targeted microbiological tests (PCR, serology). Discussing patients without the results of these tests is generally not useful, unless emergency complications occur. Information is also required with regard to:

- the medical history;
- the clinical course so far with a description of the current clinical condition of the patient;
- all treatments previously started and all previously given antibiotic agents (duration, dosing and dosing frequency);
- laboratory test results (in particular CRP, leucocyte number, kidney and liver function, levels of antibiotic agents in the blood);
- information about any intracardiac prosthetic material, if applicable (prosthetic valves, vascular prostheses, devices, etc.), including implant date and operation report (for example, about

- whether BioGlue is used);
- results of already performed additional imaging (CT, PET, MRI), as well as earlier (control) imaging of the thorax after any prosthetic valve implantation that can serve as a baseline and for comparison;
 - already performed diagnostics to identify the portal of entry (e.g. consultation of the dental surgeon, colonoscopy).

A clear description of all required data from referring centers is crucial and prevents unnecessary work for the expertise center. A short pocket manual can help, but all requested data should also be mentioned on the patient registration form.

5. What to do with acute patients?

Analogous to acute patients with severe valve failure who are not discussed in the regular heart team before they are referred, acute referral to the surgical center should also be pursued for acute patients with (suspected) endocarditis and serious complications. Serious complications include severe valve leakage, (partial) dehiscence of a valve prosthesis, or multiple septic emboli caused by large vegetations. Acute referral of these patients usually takes place via the cardiologist or thoracic surgeon on duty. Even after emergency surgery, we would advise to subsequently discuss the patient in the Endocarditis Team, in order to set indications for additional diagnostics to identify the portal of entry or extracardiac infectious foci possibly present, and to formalize further antibiotic treatment and follow-up.

6. Feedback (to referring physicians)

It is advisable to send a report to the referring physician of each patient discussed during the meeting (also for patients from the referral center itself). Relevant items to report on include the clinical course from the patient, the laboratory and culture results, a chronological overview of all administered antibiotics, results of echocardiography and additional imaging, and a summary of the discussion in the Endocarditis Team with a conclusion and proposal of a diagnostic and therapeutic management plan. It may also be valuable to collect these letters for scientific, educational and quality purposes.

The referring physician can additionally be informed about the proposed management plan concerning further diagnostics or therapy by telephone. This is especially important if this physician refers patients from another center for discussion in the Endocarditis Team, or could not attend the meeting. In addition, the EMC experienced it to be useful to directly call the medical microbiologist and/or the internist/ID specialist of the referring center (by the medical microbiologist or internist/ID specialist of the reference center), certainly if the Endocarditis Team advises another antimicrobial regimen.

Feedback in the other direction, informing all those involved in the care of the discussed patient about his/her further clinical course, is also relevant. This enables the members of the Endocarditis Team to learn by experience, too.

7. Coordination and organization

The Endocarditis Team meeting can be chaired by a medical specialist, resident or doctoral candidate, preferably the coordinator. It is important that the chairman fulfils a bridging function between all members of the Endocarditis Team and secures a broadly supported plan for management. For patients from the referral center, the treating physician of each patient should present the case during the meeting. For external patients whose referring physicians cannot attend the meeting, a medical specialist or resident from the referral center will need to get acquainted with the patient's clinical data, track down any missing data, and present this patient during the meeting of the Endocarditis Team. A doctoral candidate with a medical background and some clinical experience in cardiology and infectious diseases could fulfil this function, too. It is recommended that the person who presents the patient during the meeting, also is responsible for reporting.

Optimize the clinical care for your endocarditis patients, through multidisciplinary discussing its clinical course in a critical and cooperative Endocarditis Team within the reference center in your area!

A 32-year-old man was referred from a peripheral hospital for discussion in the Endocarditis Team. He was admitted due to a fever of 39.5 °C and chills for several days. His medical history comprises correction of a Tetralogy of Fallot with implantation of a ventricular septum defect (VSD) patch in 1986 and a pulmonary homograft in 2000. No typical clinical signs for endocarditis were present during physical examination. Blood cultures were positive for *Streptococcus oralis* (4/4 vials, MIC for penicillin 0.125 mg/L), already one day after admission. Intravenous benzyl-penicillin was started (12 grams/24 hours continuous infusion). TEE did not show any vegetations, but showed some thickening and a density on ultrasound of the intra-ventricular septum at the location of the VSD patch, referred to as calcification. The pulmonary homograft was not well assessable.

This case was discussed in the Endocarditis Team and the ultrasound images were re-evaluated. An indication to perform FDG-PET/CT was seen, in accordance with the ESC guideline⁵, because of the presence of a prosthetic pulmonary valve, the atypical findings during ultrasound examination, and the remaining uncertainty about a diagnosis of endocarditis with only positive blood cultures as major Duke criterion. Therefore, it was advised to perform a combined examination of FDG-PET with diagnostic CT angiography (CTA) at the outpatient clinic of the referral center. Additionally, it was advised to increase benzyl-penicillin (18 grams/24 hours continuous infusion) and to add gentamicin (3mg/kg, 1dd) to the antimicrobial therapy already started, as treatment of (possible) endocarditis.

FDG-PET/CTA showed a small sub-aortic cavity at the site of the VSD patch, which was new compared to previous CT-imaging of the heart, and which appeared strongly FDG-avid on the PET. Therefore, a small mycotic aneurysm was suspected. This finding was interpreted by the Endocarditis Team as consistent with infective endocarditis. As the patient responded well to the antibiotic therapy and there were no signs of shunting of blood or hemodynamic instability, it was decided to continue this conservative therapy and postpone surgery for the time being. It was advised to repeat a TTE and CTA after 6 weeks to reassess the mycotic aneurysm and evaluate the need for surgical correction.

By discussing this case in the Endocarditis Team both the diagnostic and therapeutic workups were adjusted. The patient was diagnosed with endocarditis (of prosthetic material, in this case a VSD patch) based on the information provided by additional imaging performed in the referral center and the antimicrobial treatment was adjusted accordingly.

Figure 2a: Presentation of a case study to illustrate how the Endocarditis Team can be of added value.

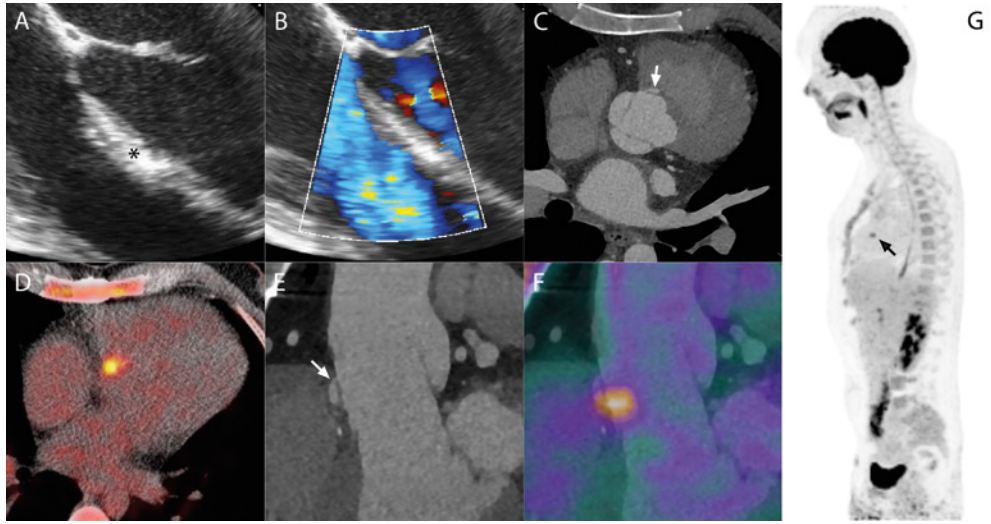


Figure 2b: Combined FDG-PET and diagnostic CTA-scan of the patient in the presented case. The transesophageal (A) and Doppler (B) view on the septum, with a clear calcified thickening at the site of the VSD-patch (asterisk), showed no evidence for a perforation of the septum (or left-right shunt). No vegetations or other signs of endocarditis were seen on the valves. However, the CTA (C, E) showed, cranially from the VSD-patch but still sub-aortal, a small opening in the intra-ventricular septum (arrow), which fills with contrast and was new compared to previous imaging after placement of the VSD-patch. The PET-scan (D, G) showed focal high-intensive FDG-uptake at the location of this small opening in the intra-ventricular septum, indicating an infectious process (mycotic aneurysm), which is clearly visible on the fused PET / CTA images (F). This enabled us to diagnose this patients with endocarditis (from the VSD patch).

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