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Endocarditis: effects of routine echocardiography during Gram-positive bacteraemia

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ABSTRACT

Background: Despite firm recommendations to perform echocardiography in high-risk patients with Gram-positive bacteraemia, routine echocardiography is not embedded in daily practice in many settings. The aim of this study was to evaluate whether a regime including routine echocardiography results in better outcome.

Methods: A total of 115 patients with Gram-positive bacteraemia and at least one risk factor for developing metastatic infection were prospectively included. Routine echocardiography was advocated and facilitated in these patients. Results were compared with a matched historical control group of 230 patients in whom echocardiography was performed at the discretion of the attending physician. Endocarditis was diagnosed according to the Duke criteria.

Results: Echocardiography was performed more often in the study group (82 *vs* 27%, p<0.001). Endocarditis was diagnosed more often among study patients, 22/115 (19%) *vs* 17/230 (7%) in the control group (p=0.002). In the study group echocardiography revealed vegetations in 22 of 94 (23%) patients, compared with 17 of 64 (27%) control patients (p=0.7). In the absence of heart murmurs, 70% of patients underwent echocardiography in the study group against 21% in the control group (p<0.001). No differences in adherence to American Heart Association guidelines concerning treatment of endocarditis were noticed. In patients with endocarditis, overall mortality was 23% in study patients and 59% in controls (p=0.04).

Conclusion: Routinely performed echocardiography in patients with Gram-positive bacteraemia resulted in diagnosing endocarditis in a larger proportion of patients, which was associated with a significant decrease in mortality rates. In the past, endocarditis was probably detected in a more advanced stage.

KEYWORDS

Bacteraemia, echocardiography, infective endocarditis, *Staphylococcus aureus*, *Streptococcus* spp

INTRODUCTION

Timely recognition of infective endocarditis is the first step in successful management and improved outcome of this potentially devastating disease. However, classical signs of endocarditis, such as new-onset heart murmurs and skin lesions, are absent in up to 57% of patients.[1,2] The importance of echocardiography to reveal cardiac sequelae has been emphasised in several studies.[3] In the American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines, echocardiography is recommended for all patients with high-risk *Staphylococcus aureus* bacteraemia to reveal disseminated disease.[4,5] Although the recommendations from the literature are clear, routine echocardiography is not performed in a substantial number of patients with *S. aureus* bacteraemia in many clinical settings: in several studies, patients with *S. aureus* bacteraemia underwent echocardiography in only 27 to 59% of cases.[2,6-9]

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We performed a unique prospective case-control study in patients with Gram-positive bacteraemia and at least one risk factor for the presence of metastatic infection comparing two echocardiographic regimes.[10-12] We added patients with Gram-positive bacteraemia because risk factors predicting the presence of metastatic infection were suggested to be identical to those in *S. aureus* bacteraemia.[13] In this prospective study, routine echocardiography was facilitated in all patients within two weeks after admission in the study group and was compared with a matched historical control group in the same hospital in whom echocardiography was performed at the discretion of the attending physician. The aim of the study was to evaluate whether routine performance of echocardiography in a high-risk patient group with Gram-positive bacteraemia leads to an increased incidence of the diagnosis of endocarditis and a better outcome when compared with clinically driven requests for echocardiography.

PATIENTS AND METHODS

Study design

This study is part of a prospective case-control study in which patients with a positive blood culture growing *Staphylococcus aureus*, *Streptococcus* species (excluding *S. pneumoniae*), or *Enterococcus* species at high risk for developing secondary metastatic foci between November 2005 and January 2008 were assigned to undergo an FDG-PET scan within 14 days after their first positive blood culture. Echocardiography was advocated and facilitated in all patients. High-risk bacteraemia was defined as the presence of at least one of the known risk factors for metastatic infectious disease, i.e., community acquisition, treatment delay for more than 48 hours after the onset of symptoms, persisting fever for more than 72 hours after initiation of antibiotic treatment, or the presence of persistently positive blood cultures for more than 48 hours after starting appropriate treatment. The original study was registered in the ISRCTN database, number 76425553. The protocol was approved by the institutional review board. Written informed consent was obtained from all patients.

All charts of subsequent adult, non-neutropenic patients with positive blood cultures were revised within the first working day in order to check for eligibility. Patients primarily admitted to the ICU were only included if they were discharged from the ICU within 14 days. Exclusion criteria were polymicrobial infection and pregnancy.

A historical control group was assigned by revising all charts of patients with the same type of bacteraemia during the four years before the study started. For this purpose, the database of the department of medical microbiology was used. Only patients with the same risk profile were eligible, including an ICU stay of less than 14 days. Matching criteria were the microorganism, community acquisition, and the presence or absence of one of the remaining risk factors. For every study patient, two of the best matching controls were included.

Endocarditis and metastatic infection

Endocarditis was defined according to the modified Duke criteria.[14] The AHA guidelines were used for the treatment of infective endocarditis. Choice and timing of starting antibiotics were evaluated in all patients diagnosed with endocarditis. No relevant changes were noticed between subsequent AHA guidelines throughout the study period.[4,15] The portal of entry of bacteraemia was defined as a localised focus of infection preceding bacteraemia. A central venous catheter (CVC) was considered a portal of entry if there was evidence of inflammation at the insertion site or if culture of the catheter tip grew the same microorganism as the blood culture in the absence of evidence for another source of infection. Metastatic infection was discriminated from the portal of entry of infection. Metastatic infection was defined as true haematogenous spreading of infection, e.g. endocarditis or spondylodiscitis. In addition, infectious foci without anatomic relations to the portal of entry or direct spreading outside the anatomic borders of the portal of entry were defined as metastatic infection, e.g., deep tissue abscess complicating a surgical wound infection.

Echocardiography

Echocardiography was strongly recommended and facilitated in all study patients by the principal investigator. Transthoracic echocardiography (TTE) was only performed first in the absence of prosthetic valves, but had to be followed by transoesophageal echocardiography (TEE) when no signs of vegetations were visualised. An echocardiogram was judged to be positive for endocarditis when vegetations, defined as oscillating intracardiac structures, were visualised on valves or their adjacent structures or in the path of a regurgitant jet, or on implanted material in the absence of an alternative anatomic explanation.[4] The outcomes of TTE and TEE were compared.

Patients

The site of acquisition of infection was determined in all patients. Bacteraemia was considered to be nosocomial if only blood cultures taken after >48 hours of hospitalisation were positive and clinical signs of the infection were absent at the time of admission. All other infections were considered community-acquired. Blood cultures were routinely taken during the first three days of admission and every second day as long as blood cultures remained positive. Except for echocardiography and FDG-PET,

which were routinely performed in all study patients, other diagnostic tests were ordered at the discretion of the attending physician. Special attention was paid to the presence of heart murmurs, immunological or vascular skin features, and the presence of guiding symptoms and signs supporting possible metastatic infectious foci. Patient follow-up ended six months after admission. Mortality data, epidemiological data, number, type and results of all diagnostic tests and treatment data were registered in a structured database (Microsoft Access).

Endpoints

The primary endpoint was the incidence of endocarditis as defined by the Duke criteria.[14] Secondary outcome measures were overall mortality, other metastatic foci of infection, and outcome of TTE and TEE.

Statistical evaluation

Differences between groups were tested with Fisher's exact tests for categorical variables. Differences for continuous variables were tested with unpaired Student t-tests. Differences were considered to be statistically significant at a p value less than 0.05 (two-sided). Cox proportional hazard models were performed to analyse outcome after adjustment for potential confounding differences between both groups. SPSS, version 17.0, was used for the analyses.

Table 1. *Baseline characteristics of study and control patients*

	Study patients % (n)	Control patients % (n)
Total number of patients	(115)	(230)
Male	56% (65)	52% (120)
Mean age (years)	59 ± 16	58 ± 16
Blood culture results:		
- *S. aureus**	64% (73)	64% (146)
- *Haemolytic streptococcus*	11% (13)	13% (29)
- *Viridans streptococcus*	15% (17)	13% (31)
- *Enterococcus* spp	10% (12)	10% (24)
Community acquisition	70% (81)	68% (156)
Treatment delay >48 hrs	27% (31)	45%[#] (104)
Persistent fever >72 hrs	46% (53)	37% (86)
Portal of entry unknown	52% (60)	46% (106)
CVC not removed within 48 hrs	5% (6)	8% (18)
Persistently positive blood cultures	16% (18)	6% (14)
Prior ICU admission	11% (13)	10% (24)
Diabetes mellitus	29% (33)	13%[b] (31)
Malignancy	14% (16)	17% (39)
Immune suppression	23% (26)	17% (39)
Prosthetic heart valves	6% (7)	4% (9)

***All *S. aureus* isolates were methicillin-susceptible. [#]p<0.05 (treatment delay was not a significant confounder for survival in a Cox proportional hazards model (not shown). p<0.05 (repetitive blood cultures were not routinely taken in the control group). No intravenous drug use was seen in the two groups.**

Table 2. *Number of patients in whom echocardiography was performed*

	Study patients (n=115)	Control patients (n=230)
TTE only	34% (39)	18% (43)*
TEE only	9% (10)	3% (7)*
TEE following TTE	39% (45)	6% (14)*
Total percentage of echocardiography	82% (94)	27% (64)*

TTE = transthoracic echocardiography; TEE = transoesophageal. p<0.05.

RESULTS

A total of 148 eligible patients with Gram-positive bacteraemia were identified during the study period. Of those, 22 were excluded because of prolonged ICU stay, and 11 refused informed consent. The remaining 115 patients were included in the study. A matched control group of 230 patients was identified out of a pool of 294 eligible patients. Baseline characteristics did not differ significantly between the two groups except for a treatment delay of more than 48 hours, which was found significantly more often in the control group, persistently positive blood cultures and diabetes mellitus, which were found significantly more often in the study group (*table 1*). Treatment delay was not a significant confounder for survival in a Cox proportional-hazards model (not shown, p=0.9). Follow-up blood culture samples had not been routinely drawn in the control group. Echocardiography was performed significantly more often in the study group (82% (94/115) *vs* 27% (64/230), p<0.001, *table 2*). In the study group two patients died before echocardiography took place, six patients refused echocardiographic evaluation and in 13 patients echocardiographic evaluation was not performed for various other reasons. The mean time between the first positive blood culture and echocardiography was 6.4 *vs* 6.8 days in the study and control group respectively, with a median of five days in both groups. Endocarditis was diagnosed significantly more often among study patients, 22/115 (19%) *vs* 17/230 (8%) in the control group (p=0.002). In the control group, endocarditis was first detected by autopsy in another two patients. Echocardiography revealed vegetations in 22 of 94 (23%) study patients in whom echocardiography was performed, compared with 17 of 64 (27%) patients in the control group (p=0.7). A negative TTE was followed by TEE in 50% of study patients (36/72) *vs* 11 of 48 control patients (23%, p=0.26). In six of 22 patients with definite endocarditis (27%), TTE did not show any signs of endocarditis while only TEE did. This was also the case in three of 17 (18%) control patients with endocarditis.

S. aureus was the causative microorganism in 13 patients with endocarditis (59%) in the study group and in eight patients (42%) in the control group (*table 3*). Seven patients in the study group had a prosthetic valve (6.1%) compared with nine patients in the control group (3.9%, p=0.42). In the study group, 4/7 of these patients were diagnosed with prosthetic valve endocarditis *vs* 3/9 in the control group (p=0.6). Only a minority of patients had vascular or immunological skin phenomena supporting a diagnosis of endocarditis: 3.5% (n=4) in the study group *vs* 0.9% (n=2) in the control group (p=0.1). Of the patients diagnosed with endocarditis, 64% had a new or existing heart murmur in the study group *vs* 79% among controls (p=0.32, *table 3*). Of the patients without a heart murmur, 71% (46/65) underwent echocardiography in the study group against 21% (39/190) in the control group (p<0.001). In patients with endocarditis, relevant metastatic foci of infection requiring supplementary therapy were found in 13 (59%) of study patients and in eight patients (42%) in the control group (p=0.54, *table 4*). In some of these patients a truly haematogenous focus of infection was the first presentation on admission, leading to repetitive echocardiography in order to identify the source of persistently positive blood cultures.

AHA guidelines concerning the choice of antibiotic treatment were followed in all study patients compared with 18 of 19 (95%, p=0.46) in the control group. Seven patients in both groups underwent valve replacement (p=0.25). The mean duration of symptoms in patients diagnosed with endocarditis before blood culture results were present was 16 days in the study group *vs* 26 in the control group. The median duration of treatment among study patients diagnosed with endocarditis was 42 (range 15 to 140) days compared with 38 (range 1 to 182) days in the control group. Two patients in the study group and six patients in the control group died within one month after admission while on antibiotic treatment. When these patients are excluded, median duration of treatment was 44 (range 13 to 140) and 42 (range 7 to 182) days, respectively. In patients without definite endocarditis or other complicating infectious foci, median treatment duration was 14 days in both groups.

Mortality rates at six months of follow-up differed significantly between the two groups in favour of the study group. Overall mortality was 19% (22/115) in study patients compared with 32% (74/230) in control patients (p=0.011). This difference was also found regarding infection-related mortality (14/115 *vs* 56/230, p=0.049). In the patients diagnosed with endocarditis during life, mortality was 23% (5/22) in the study group and 59% (10/17) in controls (p=0.04).

Table 3. *Baseline characteristics of patients with endocarditis**

	Study patients (n=22)	Control patients (n=19)
Median age (years)	58	59
Community acquisition	91% (20)	63% (12)
Duration of symptoms prior to blood culture results (mean number of days)	16	26
Unknown portal of entry	82% (18)	63% (12)
Cardiac murmur	64% (14)	79% (15)
Skin phenomena	18% (4)	11% (2)
Prosthetic valve	14% (3)	21% (4)
Microorganism		
- *S. aureus*	59% (13)	42% (8)†
- *Haemolytic Streptococcus*	9% (2)	5% (1)
- *Viridans Streptococcus*	27% (6)	42% (8)
- *Enterococcus* spp	5% (1)	11% (2)
Adherence to AHA guideline	100% (22)	95% (18)

***Endocarditis was found in 22/115 (19%) of study patients and in 19/230 (8%) of matched historical controls, p=0.005. In 2 of 19 control patients endocarditis was only diagnosed post-mortem. No right-sided endocarditis was detected. † p=0.006**

Table 4. *Other metastatic infectious foci in patients with endocarditis*

	Study patients (n=22)	Control patients (n=19)
Patient without metastatic foci	9	9
Patients with metastatic foci	13	10
- Lung	0	1
- CNS	3	2
- Endovascular	4	1
- Soft tissue	2	1
- Spondylodiscitis	3	3
- Arthritis	6	2
- Psoas abscess	1	0
- Spleen	1	0
- Eye	1	0

CNS = central nervous system.

DISCUSSION

This is the first study directly comparing two echocardiographic regimes. Routinely facilitating echocardiography in patients with Gram-positive bacteraemia resulted in the detection of significantly more patients with definite endocarditis compared with a matched historical control group in the same hospital, in whom echocardiography was ordered at the discretion of the treating physician. This was associated with significantly reduced mortality rates at six-month follow-up in the study group.

Although the recommendations to perform echocardiography have been clear for a long time, the percentage of control patients in whom echocardiography

was performed (27%) was low, completely in agreement with other population-based studies (22 to 59%).[3,6,16] The incidence of definite endocarditis in our control group (8%) is comparable with those studies (5 to 13%).[6,8,9,16] Reported incidence rates are higher (25 to 32%) in studies on selected populations in whom echocardiography was routinely performed.[17,18] No previous study, however, has directly compared two echocardiographic regimens in two identical groups, as was done in the current study. In a study on patients with *S. aureus* bacteraemia, the impact of recommendations of an infectious disease consultant were studied.[6] In patients not treated according to these recommendations (n=132), relapse rate and mortality were higher compared with patients in whom the recommendations of an infectious disease consultant were followed. In half (65/132) of patients in that study noncompliance to the recommendations concerned the failure to perform any form of echocardiography.

Although the recommendation to perform echocardiography in all patients with *S. aureus* bacteraemia is supported by both treatment guidelines and previous studies, the decision to perform echocardiography in clinical practice appears to be largely driven by the presence of certain symptoms.[1,3-5,18] This might be the most important caveat explaining the proportion of patients (18%) who did have echocardiographic examination even in our study group. This is, however, favourable compared with other studies evaluating the effects of consultation with an infectious disease specialist recommending echocardiographic evaluation in patients with *S. aureus* bacteraemia. Echocardiographic evaluation was not performed in 27 to 34% of patients in those studies.[6,9,19] In our historical control group, echocardiography was mainly restricted to patients with cardiac murmurs. Cardiac murmurs, however, were only present in 64% of patients with definite endocarditis in our prospective study group. Also, endocarditis-associated vascular and immunological phenomena of the skin and mucosa were only found in a very small minority of cases in our study group. This is in line with several other studies.[2,3,20] Patients with possible endocarditis, therefore, cannot be selected by the presence of clinical findings alone. Our findings support recommendations to perform echocardiography in all patients with *S. aureus* bacteraemia.[4,5] In previous studies, risk factors for metastatic infection in patients with other Gram-positive bacteraemia were identical to those in patients with *S. aureus* bacteraemia.[13] The present study suggests that routine echocardiography should also be performed in patients with bacteraemia caused by other Gram-positive microorganisms and at least one risk factor for metastatic complications. In 27% (6/22) of patients, infective endocarditis was only revealed by TEE following normal TTE. This is comparable with other studies (14 to 19%) comparing both echocardiographic techniques.[17,20,21]

An important difference between the present study and previous studies is that a matched control group was included in order to compare two strategies of a diagnostic approach in high-risk patients with Gram-positive bacteraemia. The use of a historical control group might have introduced potential bias. Patients were, however, accurately matched regarding risk profiles and microorganisms. In addition, the control group was large and within the timeframe of this study, no changes in diagnostic work-up or therapy regarding Gram-positive bacteraemia or endocarditis had occurred in our hospital. It is therefore most likely that endocarditis remained undetected in many control patients, as the incidence of endocarditis was significantly lower in the control group. This was also supported by the fact that endocarditis was first diagnosed by autopsy in two patients in the control group and that mortality rates were significantly higher in the control group. Autopsy had only been performed in a minority of patients in both patient groups. The antibiotic regimens for diagnosed endocarditis were similar in the two groups, regarding both choice and timing of antibiotic treatment. However, more patients in the study group underwent valve replacement. In the absence of definite endocarditis or metastatic infectious foci, no differences in treatment duration were found, suggesting that the percentage of patients with prolonged antibiotic treatment due to suspected but unproven endocarditis or metastatic foci did not differ between patient groups. Most likely early detection and intervention led to the lower mortality in patients with endocarditis in the study group, resulting in favourable mortality rates (23%) in line with previous studies (22 to 46%).[3,22] In contrast, in the past endocarditis was presumably diagnosed in an advanced stage in most patients. This was further supported by the difference in duration of symptoms prior to diagnosis. This may also be an important explanation for higher mortality rates in endocarditis patients in the past in studies on the positive effects of infectious diseases specialist consultation. An increase in the number of patients with *S. aureus* bacteraemia who underwent echocardiographic evaluation as a result of consultation with an infectious disease specialist was described in some of these studies.[6,9,19] Overall mortality rates (32%) in the control group were in line (17 to 43%) compared with studies that introduced consultation of an infectious disease specialist in order to improve diagnostics and treatment.[6,19] No details on mortality in patients with endocarditis are provided in those studies. Mortality (59%) in patients with endocarditis in the control group in the present study is in line with mortality (71 to 74%) in patients with advanced stages of endocarditis, including those with metastatic disease and congestive heart failure and patients with a contraindication for surgery.[3,22] The fact that a retrospective control group was included makes it impossible to evaluate

in detail if the non-significant difference in patients who underwent valve replacement reflects contraindications for surgery due to the advanced stage alone, or a change in acceptance for cardiothoracic surgery in the timeframe of the study. No such changes, however, were noticed in internal guidelines in our hospital.

Relevant additional infectious foci were found in more than half of patients with endocarditis. Several of these foci, such as spondylodiscitis and mycotic aneurisms, required prolonged antibiotic treatment or surgical interventions. This underscores the possibility of metastatic infectious foci being the cause of treatment failure and thus the need for a directed search for these complicating foci in addition to echocardiography. FDG-PET appears to be a valuable diagnostic technique for this purpose.[13,23]

CONCLUSION

Routine performance of echocardiography in all patients with Gram-positive bacteraemia and at least one risk factor for complicated infection is associated with the detection of a significantly higher percentage of endocarditis cases when compared with a strategy in which echocardiography was performed based on signs and clinical suspicion of endocarditis. Patients selected by a clinically driven echocardiographic regime were characterised by higher mortality rates. This probably reflects the fact that only advanced cases of endocarditis are detected relying on clinical signs and symptoms of endocarditis alone. Our results also support the finding by others that TEE is more sensitive than TTE in a substantial proportion of endocarditis patients. Therefore, transthoracic echocardiography should be performed routinely in all patients with Gram-positive bacteraemia and at least one risk factor for complicated infection. If transthoracic echocardiography does not reveal signs of endocarditis, transoesophageal echocardiography should be performed.

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