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Published in:
Clinical Infectious Diseases

DOI:
10.1093/cid/cix880

2018

Document Version:
Peer reviewed version (aka post-print)

Link to publication

Citation for published version (APA):
Sunnerhagen, T., Törnell, A., Vikbrant, M., Nilson, B., & Rasmussen, M. (2018). HANDOC - a handy score to determine the need for echocardiography in non-beta-hemolytic streptococcal bacteremia. *Clinical Infectious Diseases*, *66*(5), 693-698. https://doi.org/10.1093/cid/cix880

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5

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HANDOC – a handy score to determine the need for echocardiography in non-beta-hemolytic streptococcal bacteremia

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Keywords: Endocarditis, streptococcus, bacteremia, echocardiography, prognostic score

Running title: HANDOC and the risk for IE in bacteremia

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The HANDOC score (Heart murmur or auscultation, Aetiology, Number of cultures, Duration of symptoms, Only one species, and Community acquired infection) has high sensitivity and specificity to predict the presence of infective endocarditis in patients with non-beta-hemolytic streptococcal bacteremia.

Abstract

Background: Non-beta-hemolytic streptococci (NBHS) are a common cause of infective endocarditis (IE). Echocardiography is used to diagnose IE, but it is not known which patients with NBHS bacteremia should undergo echocardiography.

Method: Medical records of patients with NBHS bacteremia in southern Sweden from 2012-2014 were studied retrospectively. The patients were divided into two cohorts. In the first, correlations between the reported data and IE were studied. These variables were used to construct the HANDOC score, which was then validated in the second cohort

Results: 340 patients with NBHS bacteremia were included in the first cohort of whom 26 fulfilled the criteria for IE, and in 197 cases IE could be excluded. Several factors differed significantly between the patients with IE and those without. Amongst these variables, the presence of **H**eart murmur or valve disease, **A**etiology with the groups of *S. mutans*, *S. bovis*, *S. sanguinis* or *S. anginosus*, **N**umber of positive blood cultures ≥2, **D**uration of symptoms of 7 days or more, **O**nly one species growing in blood cultures, and **C**ommunity acquired infection were chosen to form the HANDOC score. With a cut-off between two and three points, HANDOC had a sensitivity of 100% and specificity of 73% in the first cohort. When tested in the validation cohort (n=399), the sensitivity was 100% and the specificity 76%.

Conclusion: HANDOC can be used in clinical decision making to identify patients with NBHS bacteremia who have a risk of IE so low that echocardiography can be omitted, therefore implementation might reduce the use of echocardiography.

Introduction

Infective endocarditis (IE) is a difficult-to-diagnose condition with diverse and unspecific symptomatology [1,2]. Non-beta-hemolytic streptococci (NBHS) have been the dominant cause of IE historically, and are still responsible for a large proportion (13-44 %) of cases [3–8]. Species determination of NBHS has been difficult, but the introduction of MALDI-TOF MS has provided a tool for secure determination, at least to the group level [9–11]. Among NBHS, the *Streptococcus mitis* group has been reported to be the most common cause of IE, the *S. mutans* and *S. bovis* groups are less common, although overrepresented in IE compared to all-cause bacteremia, and *S. salivarius* and *S. anginosus* groups are underrepresented as causes of IE [8,12,13]. Blood cultures and trans-esophageal echocardiography (TEE) are the cornerstones in the diagnosis of IE [14,15].

In addition to IE, NBHS are known to cause other types of invasive infections such as abscesses [13,16,17], neutropenic fever [18,19], and bacteremia in neonates [20]. The risk factors for IE in patients with NBHS bacteremia have not been studied systematically, although prior dental surgery has been associated with a higher risk of IE and neutropenia with a lower likelihood of IE [21]. In bacteremia caused by *Staphylococcus aureus*, persistent bacteremia, community acquired infection, and the presence of prosthetic valves or cardiac implantable devices are associated with IE [22,23] and these features have been employed to form scoring systems such as PREDICT and VIRSTA-score which help to determine the need for echocardiography [22,24]. For enterococcal bacteremia a scoring system termed NOVA can guide the use of TEE [25], and an adapted form of the NOVA score has been validated [26]. There are no scoring systems available to help clinicians determine whether or not to perform TEE when presented with a patient with NBHS bacteremia. To rectify this we conducted a retrospective survey to establish the risk factors for IE in patients with NBHS bacteremia and formulate a risk stratification score for IE.

Methods

Study design

Two cohorts of patients with NBHS bacteremia were studied retrospectively. A list of blood cultures positive for NBHS from 977 individual, consecutive patients was received from the Department of Clinical Microbiology in Lund, Sweden. The laboratory is the only clinical microbiology laboratory in a geographically defined administrative region, with 1.3 million inhabitants. Patients under 18 years of age, those with inaccessible patient charts, or those with neutropenia were excluded. The inclusion was made into one of two cohorts, the first with patients cultured between the 1st of January 2012 and the 30th of June 2013, the second with patients cultured between the first of July 2013 and the 31st of December 2014. The first group was used to assess general patient characteristics and outcomes, and to generate the scoring system. The second group of patients was used to validate the scoring system. The BacT/Alert blood culture system (bioMérieux, Marcy l'Etoile, France) was used and identification of the bacteria was done to the group level [27] using MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) as described previously [12]. The bacteria were categorized into seven groups; the *Streptococcus anginosus* group, the *Streptococcus bovis* group, the *Streptococcus sanguinis* group, the *Streptococcus mitis* group, the *Streptococcus mutans* group, the *Streptococcus salivarius* group and other NBHS [28,29] (for details see supplementary data 2). *S. pneumoniae*, though a member of the *S. mitis* group, was not included in this study. Bacterial isolates that were reported as NBHS without species or group (n=130) were re-assessed with Ultraflextreme MALDI-TOF MS, using the MALDI Biotyper version 3.1 software with MBT Compass Library, DB-6903 MSP (Bruker Daltonics, Bremen, Germany) on stored isolates. A score of 2.0 or greater was required for group identification [9,12].

Assessment of medical records

The medical records of the first cohort were reviewed according to a pre-defined protocol (Appendix 1). The procedure was approved by the local committee for research ethics (2013/13). Patients were considered to have IE if they fulfilled the modified Duke criteria [30] or were diagnosed with IE at autopsy. Patients were placed in the negative group if: a) TEE had been performed without signs of IE, b) if they received less than 14 days of intravenous antibiotics or 21 days of antibiotics in total and survived for at least six months

without relapse of bacteremia, or c) had no signs of IE at autopsy. Patients who did not meet the criteria for the positive or negative group fell into the unknown category.

Validation cohort

Data from the patients in the validation cohort was gathered after the score was finalized. The number of parameters included was limited to general patient demographics, the variables included in the chosen risk stratification model, and the data necessary to confirm or deny the presence of IE.

Data analysis

Statistical analysis was performed using SPSS Statistics 24 (IBM) and MedCalc (MedCalc software bvba). Patients with confirmed IE or confirmed absence of IE were compared using Mann Whitney U or Fisher's exact test. Since the testing was made to generate candidate variables for the odds ratio testing, no correction for multiple testing was done. Univariable odds ratio calculations were performed on variables that were candidates for the scorings systems.

Results

Main cohort

Between the 1st of January 2012 and the 30th of June 2013, blood cultures from 446 patients with growth of NBHS were recorded. After excluding persons under 18 years of age (n=54), neutropenic patients (n=31) and those where medical records were not accessible (n=13), 348 patients remained. Nine isolates that had not previously been identified to the species level were excluded as they were not NBHS. When analyzing the remaining patients, 26 cases of IE and 197 cases of non-IE were identified, the remainder were unknown (figure 1).

Demographics and diagnoses

Demographic variables are presented in Table 1. Patients with IE had experienced symptoms for a significantly longer period at the time when the blood culture was taken ($p<0.0001$). Some factors were significantly more common in the group with IE, including community-acquired infection ($p=0.02$), pre-existing heart valve disease ($p<0.001$), and heart murmur upon auscultation ($p<0.001$). Embolic events were more common in the IE group, but this

difference was not significant (p=0.2). The presence of fever was similar in those with confirmed or excluded IE.

Microbiology

Table 2 summarizes the microbiological findings. Streptococci of the *S. sanguinis* group were the most common cause of IE (11 of the 26 confirmed cases), followed by *S. bovis* group (5 cases), *S. mutans* group (4 cases), *S. mitis* group (4 cases) and *S. salivarius* group (2 cases). No IE-cases in this cohort were caused by *S. anginosus* group isolates. Compared to the non-IE group, *S. sanguinis* (p=0.001) *S. bovis* (p=0.03), and *S. mutans* (p=0.007) group streptococci were overrepresented in the IE-group, and *S. anginosus* group streptococci were underrepresented (p<0.001). A detailed account of group and species distribution is given in Appendix 3. Having a single bacterial species in the blood culture was more common in the IE group (p<0.001). The number of positive blood cultures was higher in the IE group (p<0.001), with a median of two positive compared to one in the non-IE group. The presence of continuous bacteremia was also significantly higher (p=0.002) in the group with confirmed IE.

Management and outcome

Table 3 shows patient outcome and clinical management. Neither the 30-day all-cause mortality nor the 6-month all-cause mortality differed significantly between cases with confirmed or excluded IE A higher proportion of patients in the IE group had undergone TEE or TTE.

Risk factors for IE and the HANDOC score

Several factors that differed significantly between the IE and non-IE group were tested for their suitability in a scoring system. Using such variables, the HANDOC risk score was chosen, with parameters that were common and differed significantly between patients with and without IE. The score is presented in Table 4.

Figure 2 shows a receiver operator characteristics (ROC)-curve of the HANDOC-score using the patients with and without IE. The area under the curve is 0.96 (95% CI 0.93-0.98) using a binomial exact confidence interval. With a sensitivity of 100% (95% CI 88-100) and specificity of 73% (95% CI 67-80), the cut off was set between 2 and 3 points. There was no significant difference in specificity between men (73%) and women (74%). When the

HANDOC score was tested against the whole cohort (including also the unknown category), the performance of the score was similar (75% specificity, AUC of the ROC curve 0.96) to when applied only to IE and non-IE cases. The resulting negative predictive value was 100% and the positive predictive value was 23% with the prevalence of 7.6% as in the main cohort.

Validation cohort

Between the 1st of July 2013 and the 31st of December 2014, blood cultures with NBHS from 522 patients were received. The inclusion and exclusion of patients is presented in Appendix 3. HANDOC was applied to the patients with (n=37) and without IE (n=264) and using a cut-off score of ≥3 the resulting sensitivity was 100% (95% CI 91-100) and the specificity was 76% (95% CI 71-81). When HANDOC was applied to the entire validation cohort, including also the unknown group, 77% of the cases without confirmed IE had a score of ≤2 points.

Consequences of HANDOC on the need for echocardiography

Echocardiography was performed on 42% of all patients in the two cohorts. 30% of the patients with a HANDOC score of 2 or less and 69% of the patients with a HANDOC score of 3 or more underwent echocardiography. If HANDOC had been used to guide the need for echocardiography, the investigation would have been performed on 31% of the patients. As a subpopulation analysis we applied the HANDOC score in patients where echocardiography of any kind was performed and the resulting sensitivity was 100% and the specificity 62%. Including only the cases where TEE was performed, the sensitivity was 100% and the specificity was 47%.

Discussion

In our clinical setting, IE is relatively uncommon (8.5%) in bacteremia with NBHS. However, the suspicion of IE is often raised in this condition and clinicians need tools to determine which patients should undergo echocardiography. We suggest the HANDOC score to guide the use of echocardiography. This score includes parameters that differ significantly between patients with confirmed and excluded IE, that are relatively common among patients with IE, and are easily accessible for the clinician. With the established cut-off of 3 points, HANDOC had excellent sensitivity (100 %) and good specificity (74 %) in the first cohort. Importantly

the specificity was similar for men and women and was also unaffected by inclusion of the group of patients where IE could formally not be ruled out. Thus HANDOC is a well-suited tool for its purpose when applied to the cohort in which it was created. To validate the score, we applied it in the second cohort of patients and found it to be highly sensitive (100 %) and specific (76 %). Neither the PREDICT nor the NOVA score were validated in the original publications [22,25] and it is a major advantage that we could herein confirm the suitability of HANDOC in another cohort of patients. The NOVA-score was later validated in a different cohort of patients [26] and the HANDOC score would also benefit from further external validation. The fact that both the score creation and the score validation cohorts consisted of patients from the same geographical area and from the same hospitals is a limitation of the study and makes it difficult to draw definite conclusions about the suitability of the score in other settings.

The "Heart murmur or valvular disease" and "Aetiology" criteria are similar to those included in the Duke criteria, and the "Number of cultures"-criterion of HANDOC is included in the Duke criteria. However, "Duration of symptoms", "Only one species", and "Community acquired" are parameters not part of the Duke criteria. Some features of the Duke criteria were deemed not to be suited for inclusion in our score. Fever was not discriminatory between cases with and without IE whereas embolization was indicative of IE. Embolization was, however, uncommon and the retrospective nature of our study made it difficult to reliably determine if embolization was present at the time where HANDOC would have been applied. We thus chose not to include signs of embolization in the score, but the presence of septic emboli should of course alert the clinician to the risk of IE regardless of HANDOC score, and a low HANDOC score should not withhold the use of echocardiography in patients where the clinician has other reasons to suspect IE.

In the univariable analysis, both the presence of Heart murmur and underlying heart disease were associated with IE but we chose to combine these variables as they are strongly interconnected mechanistically and were significantly correlated ($p<0.0001$ using two-tailed Pearson's test). A long duration of symptoms is a textbook description of NBHS IE and was found to be highly indicative of IE in our investigation and should clearly be included in a scoring system. Only one species is also highly motivated since it is the rule in IE. Community acquisition is a typical feature of IE caused by *S. aureus* [31] and is part of the PREDICT scoring system [22]. The association of community acquisition also with NBHS IE

in our study made it reasonable to include this variable in the score. The retrospective design of the study makes it sensitive to systematic biases. For example, a physician who strongly suspects IE might be more prone to record a long duration of symptoms and more prone to take additional blood cultures. This might increase the likelihood of a recorded long duration of symptoms ("D" in HANDOC) and of having more than two positive blood cultures ("N" in HANDOC). The number of positive cultures and number of cultures taken correlated significantly in our study ($p<0.0001$ with two-tailed Pearson's correlation). We therefore compared the number of positive cultures in a subgroup where two cultures had been taken (n= 180). The number of positive blood cultures in this subgroup was significantly higher ($p<0.0001$, Fisher's exact test) in the group with IE than in the group where IE had been excluded. The finding of an NBHS in a single flask in a set of blood cultures is by some clinicians regarded as a contamination and no further consideration of the finding is made. We did not find cases of IE with growth of NBHS in only one flask but the HANDOC score was ≥3 in only 18 such cases, the majority of which had long duration of symptoms, heart murmur on auscultation, or pre-existing heart valve disease. In our experience IE occurs also in patients with a single positive flask and such a finding should not preclude the patient from echocardiography guided by a risk-stratification using HANDOC.

A limitation of this study is that the group of patients with IE was too small to allow multi-variable analysis. Thus it may well be possible that the variables associated with IE in our analyses are not truly directly linked to the outcome. Irrespective of causality, however, a model using simple variables, such as HANDOC, might be more robust than sophisticated models using more information [32,33]. The microbiological variables Aetiology, Number of cultures and Only one species may typically not all be independently associated with IE, but as they are easily accessible and work well in the model we find it reasonable to include them anyway. After careful consideration we chose to suggest that an *S. anginosus* group NBHS should subtract one point from the score despite the possibility that this makes the score more complicated to use. We chose to make the analyses on the group of NBHS since the MALDI-TOF MS method is robust for group identification but not necessarily for determination of all species [9]. This conservative approach makes the application of the score easier in other contexts but it risks missing the possibility that certain species of NBHS might be over- or under-represented in IE. An interesting finding is the high proportion of IE in cases of bacteremia with *S. sanguinis* group streptococci, which is in contrast to previous findings by our group where *S. mitis* group streptococci were the most common cause [12]. The reason

for this is most probably that the *S. sanguinis* group previously has been included in the *S. mitis* group.

We chose to exclude patients with neutropenia due to several lines of argument. NBHS bacteremia in neutropenic patients has been argued to be a very different entity of infection [34] which has led to a wide-spread notion that such patients are not at risk for IE. This is supported by the fact that IE with NBHS, to our knowledge, has not been reported in patients with neutropenia. Since few of the patients with neutropenia had undergone TEE and most had received long antibiotic treatments, almost all patients with neutropenia would have been classified into the unknown group.

Implementing HANDOC as a guide for when to use echocardiography in NBHS bacteremia would presumably reduce the overall number of investigations and direct the use towards patients with a higher risk of IE. If echocardiography had only been performed in the cases with a HANDOC score of 3 or more, the total number of investigations would have been decreased from 307 to 225. In our study the number needed to screen to find one case of IE was 3.6.

In summary, HANDOC is an easy-to-use score to be utilized when a clinician is alerted to a blood culture containing NBHS. Three of the six criteria are available directly in the report from the microbiological laboratory, interviewing the patient assesses two and the final point is auscultatory or anamnestic. The HANDOC score has an excellent sensitivity and high specificity that should make it useful in clinical practice.

Funding

This work was supported by the Swedish Government Fund for Clinical Research (ALF), the Royal Physiographic Society in Lund, the Marianne and Marcus Wallenberg foundation, the Crafoord foundation, the Alfred Österlund foundation, the Anna-Lisa & Sven-Erik Lundgren foundation, the Sigurd & Elsa Golje foundation, and the Längman foundation.

Acknowledgements

We acknowledge the help by Mrs. Lena Hyllebusk, Dr Malin Inghammar, Dr Oonagh

Shannon, and Dr Susann Ullén for important discussions. Parts of this work has been presented orally at the meeting for infectious diseases specialists in Karlskrona, Sweden, and at the 14th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections (ISCVID) in Dublin, Ireland, June 2017.

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Table 1. Clinical characteristics

	All cases n=339	IE confirmed n=26	IE excluded n=197	P-value, IE confirmed vs excluded
Age, median (range)	74 (20-10)	65 (24-91)	73 (20-96)	0.1
Gender, number male (%)	190 (56)	21 (81)	116 (59)	0.03
Charlson score, median (range)	2 (0-11)	1.5 (0-7)	2 (0-11)	0.8
Community acquired, no (%)	145 (43)	19 (73)	94 (48)	0.02
Health-care associated, no (%)	143 (42)	4 (15)	76 (39)	0.03
Nosocomial, no (%)	51 (15)	3 (12)	27 (14)	1.0
Duration of symptoms, days, median (range)	1 (0-114)	16.5 (0-114)	1 (0-61)	<0.001
Previous IE, no (%)	3 (1)	1 (4)	0 (0)	0.1
Pacemaker, no (%)	18 (5)	4 (15)	10 (5)	0.07
Heart valve disease, no (%)	46 (14)	15 (58)	18 (9)	<0.001
Heart murmur, no (%)	70 (21)	16 (62)	33 (15)	<0.001
Fever, no (%)	229 (68)	21 (81)	145 (74)	0.6
Embolization, no (%)	8 (2)	2 (8)	3 (2)	0.05

Table 2. Microbiological data

	Overall n=339	IE confirmed n=26	IE excluded n=197	P-value, difference between IE confirmed and excluded
***S. mitis* group, no (%)**	102 (30)	4 (15)	61 (31)	0.1
***S. sanguinis* group, no (%)**	52 (15)	11 (42)	28 (14)	0.001
***S. bovis* group, no (%)**	27 (8)	5 (19)	11 (6)	0.03
***S. anginosus* group, no (%)**	105 (31)	0 (0)	64 (33)	<0.001
***S. mutans* group, no (%)**	9 (3)	4 (15)	4 (2)	0.007
***S. salivarius* group, no (%)**	35 (10)	2 (8)	25 (13)	0.8
Other NBHS, no (%)	19 (6)	1 (4)	12 (6)	1.0
Number of positive cultures, median (range)	2 (1-8)	2 (1-7)	1 (1-8)	<0.001
Continous bacteremia, no (%)	12 (4)	5 (19)	5 (3)	0.002
Only one species in culture, no (%)	213 (63)	25 (96)	123 (62)	<0.001

Continuous bacteremia was defined as the finding of the same bacterial isolate during the episode at least one day after the first culture taken

Table 3. Management and outcome

	All cases n=339	IE confirmed n=26	IE excluded n=197	P-value, IE confirmed vs excluded
Death within 30 days, no (%)	48 (14)	1 (4)	5 (3)	0.5
Death within 6 months, no (%)	97 (29)	4 (15)	11 (6)	0.08
Days hospitalized, median (range)	9 (0-139)	21 (0-45)	8 (0-139)	<0.001
Length of antibiotic treatment, median (range)	13 (0-150)	28 (0-95)	12 (0-150)	<0.001
TTE performed, no (%)	118 (35)	24 (92)	70 (36)	<0.001
TEE performed, no (%)	72 (12)	22 (85)	49 (25)	<0.001

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439 **Table 4.** The HANDOC score

Variable	Components of score	Univariate Association Odds Ratio for cases with IE vs IE excluded (95% CI) [p-value]
<u>H</u>eart murmur or valvular disease. One point for the presence of a valvular disease or prosthesis or the finding of a heart murmur.	Heart murmur	8.0 (3-19) [<0.001]
	Heart valve disease	14 (5-34) [<0.001]
	Heart murmur or heart valve disease	20 (6.6-62) [<0.001]
<u>A</u>etiology. One point if the species is in the *S. bovis*, *S. sanguinis* or *S. mutans* group. Subtract one point if in *S. anginosus* group. Other streptococcal groups neither give nor subtract points.	*S. bovis* group	4.0 (1.3-13) [0.02]
	S. mutans group	8.8 (2-38) [0.003]
	S. anginosus group	0.039 (0.002-0.7) [0.02]
	S. sanguinis group	4.4 (2-11) [<0.001]
	S. mitis group	0.4 (0.1-1.2) [0.1]
	S. salivarius group	0.6 (0.1-2.6)[0.5]
<u>N</u>umber of cultures. One point if the number of blood cultures containing NBHS is two or more.		45 (6-340) [<0.001]
<u>D</u>uration of symptoms One point if the duration of symptoms is seven days or more		13 (5-33) [<0.001]
<u>O</u>nly one species One point if there is only one bacterial species in the blood cultures		42 (5-310) [<0.001]
<u>C</u>ommunity acquired One point if the infection is community acquired		3.0 (1-7) [0.02]

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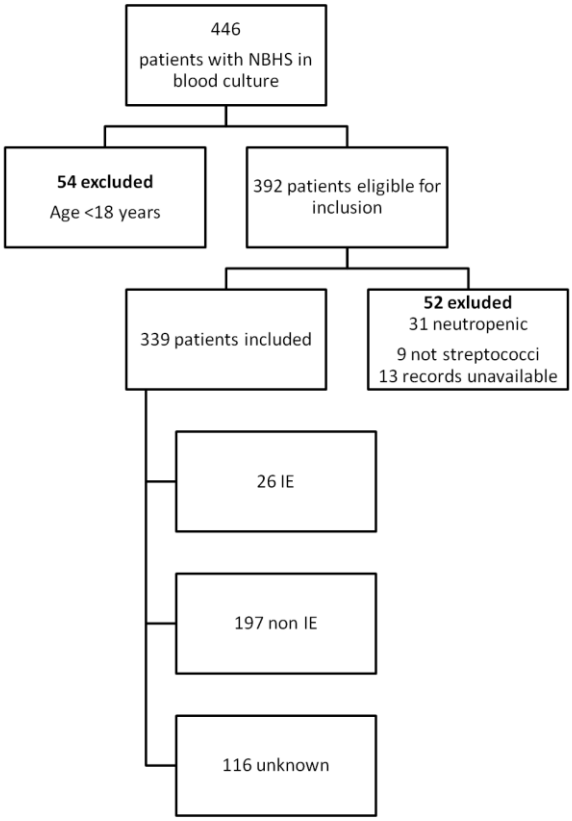

Figure 1. Flowchart of inclusion and exclusion in the first cohort.

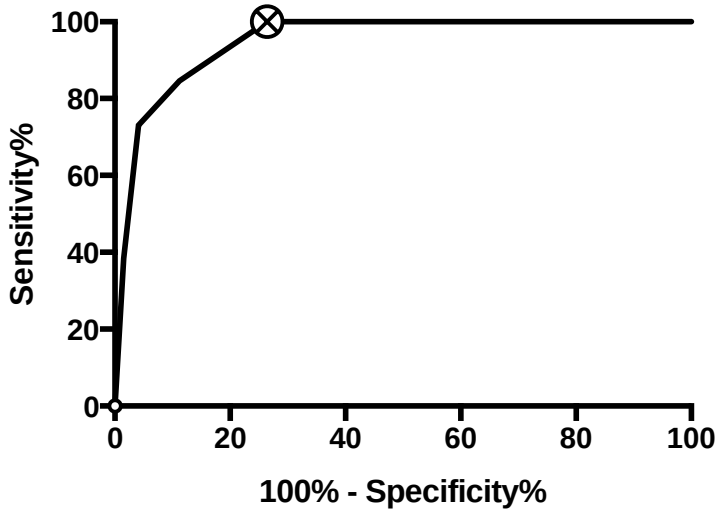

Figure 2. Receiver operator curve for HANDOC in the first cohort, excluding patients with unknown status.