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Short communication

Non-HACEK Gram-negative bacillus endocarditis

Endocardite à bacilles à Gram négatif non HACEK

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Abstract

Patients and methods. – Retrospective analysis of clinical data using 26 diagnosed non-HACEK Gram-negative infective endocarditis cases from nine hospitals in Turkey.

Results. – Mean age of patients was 53 (28–84) years, with a 23% case fatality. Nineteen (73%) of the 26 patients had at least one predisposing factor. The presence of a central venous catheter was the most common predisposing factor (7/26 patients). *Pseudomonas aeruginosa* (7/26 patients) and *Escherichia coli* (7/26 patients) were the most common pathogens. The median duration of the antibiotic therapy was 42 days (range 3–84 days). Surgical procedures were performed in 10 patients. The case fatality was similar in patients who did or did not undergo surgery (20% vs. 25%).

Keywords: Endocarditis; Catheterization; Gram-negative bacteria

Résumé

Patients et méthodes. – Analyse rétrospective des données cliniques sur 26 cas d'endocardite infectieuse à bacilles à Gram négatif non HACEK dans neuf hôpitaux turcs.

Résultats. – L'âge moyen de la cohorte de patients était de 53 ans (28–84 ans). La létalité était de 23 %. Parmi les 26 patients, 19 (73 %) avaient au moins un facteur prédisposant. La présence d'un cathéter veineux central était le facteur prédisposant le plus fréquent (7/26 patients). *Pseudomonas aeruginosa* (7/26 patients) et *Escherichia coli* (7/26 patients) étaient les pathogènes les plus fréquents. La durée médiane de l'antibiothérapie était de 42 jours (3 à 84 jours). Des interventions chirurgicales ont été réalisées chez 10 patients. La létalité était similaire chez les patients ayant ou non subi une intervention chirurgicale (20 % vs 25 %).

Mots clés : Endocardite ; Cathétérisme ; Bactéries à Gram négatif

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1. Introduction

Infective endocarditis (IE) is an uncommon but severe infection associated with high morbidity and case fatality [1]. Despite improvements in healthcare and treatment options, the diagnosis and management of IE remain challenging. Viridans streptococci and *Staphylococcus aureus* are the most common bacterial agents of IE, followed by enterococci and HACEK group bacteria [2–5]. Gram-negative bacteria rarely cause IE because of their relatively low endocardial affinity. The frequency of IE due to non-HACEK Gram-negative bacteria was reported at approximately 1% in a multinational study [6].

Intravenous drug use has been considered for decades as the most common predisposing factor for non-HACEK Gram-negative IE until recent studies and registries reported different results [6–8]. Increasing vascular catheterization and elderly population may be new risk factors for non-HACEK Gram-negative IE.

Data on non-HACEK Gram-negative IE is limited to case reports and case series. There is a need for more studies considering the increasing and changing epidemiological risk. We aimed to contribute to the report of clinical characteristics, management, and outcome of non-HACEK Gram-negative IE.

2. Methods

We performed a retrospective, multicenter, and observational study between 2007 and 2016. Adult patients with a diagnosis of non-HACEK Gram-negative IE were included in the study. Individual patient files were searched to obtain demographic and clinical data. Using emails, we invited infectious disease specialists to take part in the study. Nine tertiary hospitals agreed to participate. Hospitals were sent a case record data file (Microsoft Excel form) and were asked to fill it out. The following data was obtained for all patients presenting with Gram-negative endocarditis: age, gender, known predisposing factors, symptoms, clinical presentation, echocardiogram findings, microbiological test results, treatment preferences, complications, and history of drug use. Participating hospitals were asked to report any other endocarditis case observed over the past 10 years and the proportion of Gram-negative endocarditis cases was calculated.

Following obtention of data records, the diagnosis of patients was reviewed according to the modified Duke criteria [9]. Ten patients were excluded from the study: four because of a lack of echocardiogram findings, and six because of the identification of endemic pathogens (*Brucella*) and HACEK group bacteria.

Numerical data is presented as mean ± SD or median (IQR and range). Categorical data is presented as number and percentage.

3. Results

3.1. Patients' characteristics

Twenty-six patients (53 ± 14 years [range: 28–84], 15 [58%] females) presenting with non-HACEK Gram-negative IE were assessed. Nineteen (73%) of them had at least one of the predisposing factors considered in the study. None of them were intravenous drug users. One patient had a history of IE. Rheumatic valve disease ($n = 4$) and prosthetic valves ($n = 2$) were the most frequent structural valve diseases. Demographic, clinical, and treatment features of the study population are detailed in Table 1.

All 26 cases were confirmed as definite endocarditis according to the modified Duke criteria: 26 (100%) were confirmed by both major blood culture criteria and major echocardiographic criteria. The frequency of modified Duke criteria is detailed in Table 2.

Intravascular catheterization was observed in seven patients: three patients had a short-term central venous line and four patients had a hemodialysis catheter. All catheterization sites were the internal jugular vein. The presence of a heart murmur was detected in 21 patients (80%). The most common symptoms were chills and fever. The median duration of fever before diagnosis was 11 days (IQR; 5–14 days). None of our study patients had Janeway lesions and/or Osler's nodes. Splinter hemorrhages were observed in one patient and Roth's spot in two patients. Erythrocyte sedimentation rate (ESR) was measured in 22 patients. The mean ESR was 67 ± 32 and 80% of ESRs were □50 mm/h. Transthoracic echocardiography (TTE) was performed in all patients, and 20 of them were further evaluated with transesophageal echocardiography (TEE). Embolic events were observed in six patients (23%). The major site for embolic events was the brain ($n = 5$). One patient developed septic arthritis and one patient experienced pulmonary septic emboli. Hematuria was detected in 9/25 (36%) patients.

Overall, the study included five (19%) patients presenting with prosthetic valve endocarditis and 21 (81%) patients presenting with native valve endocarditis. Of the 26 patients presenting with non-HACEK Gram-negative IE, eleven (42%) had mitral vegetation, five (19%) had tricuspid vegetation, and six (23%) had aortic vegetation. Aortic dehiscence was observed in three patients (12%). One of the 26 (4%) patients had intracardiac device-associated (ICD) vegetations. The largest vegetation size was 20 mm and the median size was 11 mm (5–20 mm).

3.2. Microbiological data

The microbiological spectrum and drug resistance pattern of non-HACEK Gram-negative IE in the study population are detailed in Table 3

. At least two blood culture sets were drawn in each of the 26 patients. All patients had at least one positive blood culture set (the mean number of drawn blood cultures in each patient with a preliminary diagnosis of IE was 5, and an average of four of them gave positive results).

3.3. Treatment and outcomes

IE diagnosis was made after a median of seven days (IQR: 3–11 days) following hospitalization. The median duration of the antibiotic therapy was 42 days (range 3–75 days). Fever usually resolved within seven days of an effective antibiotic therapy.

Cardiovascular surgical procedures were performed in 10 patients during hospitalization (valve replacement in nine

Table 1
Demographical, clinical, and treatment features of Gram-negative endocarditis cases.
Paramètres démographiques, cliniques et thérapeutiques des cas d'endocardite infectieuse à bacille à Gram-négatif.

Age, gender	Predisposing conditions	Pathogens	Antibiotics	Echocardiogram findings	Surgical intervention	Outcome
36, M	None	*Pseudomonas mendocina*[a]	Ceftazidime + amikacin	Mitral vegetation	Yes	Alive
41, M	None	*P. aeruginosa*	Ceftazidime + amikacin	Mitral vegetation	Yes	Alive
51, M	Aortic valve replacement, mitral valve replacement	*Salmonella enteritidis*	Penicillin g + gentamicin	Mitral vegetation, heart failure	Yes	Alive
52, F	Mitral valve replacement	*Escherichia coli*	Ofloxacin	Mitral vegetation	No	Alive
58, M	Atrial septal defect, ventricular septal defect, prosthetic valve	*Enterobacter cloacae*	Imipenem/cilastatin	Aortic valve dehiscence, heart failure	No	Alive
68, M	Central venous catheter, hemodialysis, immunocompromised	*E. coli*	Piperacillin-tazobactam	Aortic vegetation, heart failure	No	Alive
48, F	Immunocompromised, liver transplant	*S. enteritidis*	Ciprofloxacin	Mitral vegetation	Yes	Alive
67, F	Immunocompromised, prosthetic valve	*Klebsiella pneumoniae*	Meropenem	Aortic vegetation, heart failure	No	Death
51, M	Central venous catheter, intracardiac device	*E. cloacae*	Piperacillin/tazobactam + cefepime	Vegetation on intracardiac device, heart failure	No	Alive
44, F	None	*E. coli*	Ceftriaxone	Mitral vegetation, heart failure	No	Alive
45, M	Previous endocarditis	*Pasteurella multocida*	Amoxicillin	Valve dehiscence	No	Alive
58, F	Central venous catheter	*K. pneumoniae*	Imipenem/cilastatin + amikacin	Tricuspid vegetation	No	Alive
67, F	Immunocompromised	*E. coli*	Amoxicillin	Mitral vegetation	No	Alive
66, F	None	*E. coli*	Ceftriaxone	Aortic vegetation, heart failure	Yes	Alive
33, F	None	*K. pneumoniae*	Ceftriaxone + gentamicin	Mitral vegetation	No	Death
36, M	Central venous catheter, hemodialysis	*P. aeruginosa*	Imipenem/cilastatin	Tricuspid vegetation	Yes	Alive
84, F	Central venous catheter, hemodialysis	*E. coli*	Imipenem/cilastatin	Tricuspid vegetation	No	Death
56, F	Central venous catheter, immunocompromised	*K. pneumoniae*	Ceftazidime + tigecycline	Tricuspid vegetation	Yes	Alive
42, F	Aortic valve replacement, mitral valve replacement	*K. pneumoniae*	Ceftriaxone + gentamicin + rifampicin	Aortic vegetation	No	Alive
59, F	Central venous catheter, hemodialysis	*P. aeruginosa*	Meropenem	Tricuspid vegetation	No	Alive
64, M	Post-coronary angiography	*P. aeruginosa*[a]	Ceftazidime + amikacin	Mitral vegetation	No	Alive
61, M	Post-coronary angiography	*P. aeruginosa*[a]	Ceftazidime + amikacin	Mitral vegetation, heart failure	Yes	Death
28, F	Post-coronary angiography, aortic valve replacement	*P. aeruginosa*[a]	Meropenem + amikacin	Aortic valve dehiscence, heart failure	Yes	Death
40, M	Rheumatic heart valve disease	*S. enteritidis*	Ceftriaxone	Aortic vegetation, heart failure	Yes	Alive
47, F	None	*E. coli*	Vancomycin + gentamicin	Aortic vegetation	No	Alive
80, F	Hemodialysis	*P. aeruginosa*	Not available[b]	Mitral vegetation	No	Death

[a] Previously published case reports.
[b] The patient died within 3 days.

Table 2
Frequency of Duke Criteria among 26 patients presenting with non-HACEK Gram-negative bacillus endocarditis.
Fréquence des critères de Duke chez 26 patients présentant une endocardite à bacille à Gram-négatif non-HACEK.

Criteria	Frequency *n/n* (%)
Major blood culture criteria	26/26 (100%)
Major echocardiographic criteria	26/26 (100%)
Minor criteria	
Predisposing factor	19/26 (73%)
Fever	20/26 (77%)
Vascular signs	6/26 (23%)
Immunological signs	2/26 (8%)
Microbiological criteria	0/26 (0%)

Table 3
Microbiological spectrum and drug resistance pattern of non-HACEK Gram-negative infective endocarditis in the study population.
Spectre d'activité microbiologique et résistance des endocardites infectieuses à bacille à Gram-négatif non-HACEK de la population à l'étude.

Bacteria	Frequency, *n* (%)	Drug resistance pattern
E. coli	7 (26)	6/7 pan-susceptible, 1/7 MDR
P. aeruginosa	7 (27)	7/8 pan-susceptible, 1/8 MDR
P. mendocina	1 (3)	
K. pneumoniae	5 (19)	2 pan-susceptible, 2 MDR, 1 XDR
S. enteritidis	3 (10)	Pan-susceptible
E. cloacae	2 (8)	2 MDR
P. multocida	1 (4)	Pan-susceptible

MDR: multidrug-resistant; XDR: extensively drug-resistant.

patients and valve repair in one patient). The median time to surgery after initial diagnosis of IE was 24 days (range 5–54 days). Five (50%) of 10 patients who underwent surgical procedures had positive valve (vegetation) cultures (*P. aeruginosa* in two patients). Six patients (23%) died during the hospitalization period. Case fatality (2 of 10 patients with medical treatment only vs. 4 of 16 patients with surgical and medical treatment) did not differ significantly.

Six hospitals were able to provide the number of endocarditis cases. Among all endocarditis cases, the proportion of Gram-negative endocarditis was 1%.

4. Discussion

Endocarditis is a chronic infection resulting from the interaction between bacterial virulence (adherence, biofilm) and endocardial endothelial surface [10]. Non-HACEK Gram-negative bacteria do not usually cause endocarditis due to their limited ability to form biofilms and low affinity to endocardial endothelium, except for *Salmonella* spp. [11]. A small number of strains of non-HACEK Gram-negative agents capable of forming biofilms might be the causative agents of endocarditis with the help of predisposing factors (valve abnormalities and prosthetic materials) that can facilitate the persistence of the microorganism within the vegetation [12]. *Pseudomonas* species can cause community-acquired and nosocomial endocarditis [13]. In our study three *P. aeruginosa* endocarditis cases developed after coronary angiographic intervention due to contamination of the contrast medium in a tertiary hospital. *Salmonella* species are also rare pathogens responsible for infective endocarditis [14]. While environmental pathogens are pan-susceptible to antimicrobials, *Klebsiella* endocarditis is associated with a higher risk of drug resistance.

The most prominent risk factor for non-HACEK Gram-negative IE observed in our study was determined by the presence of an intravascular catheter, as recently reported [5–7]. Permanent central venous catheters (e.g., hemodialysis catheters) are associated with a higher risk of developing Gram-negative endocarditis, especially in immunocompromised patients. Previous studies reported intravenous drug use as the most prevalent risk factor for non-HACEK Gram-negative IE [7,8]. Intravenous drug use was not observed in our study population. On the basis of underlying valve diseases (rheumatic valve disease, degenerative valve disease, and the presence of prosthetic valve), the predisposing condition distribution was similar to the results of previous studies [5–7].

The dynamic epidemiological changes in both host- and pathogen-related factors are new challenges for clinicians. IE patients are now older and have more comorbid conditions [15]. According to the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) results, healthcare contact and implantation of endovascular devices are primary risk factors for non-HACEK Gram-negative IE [5,6]. Seventeen patients in our study had underlying diseases that related to at least one surgical (valve replacement, catheterization) or medical (chemotherapy, hemodialysis) intervention.

The case fatality observed in our study was similar between patients who did or did not undergo surgical therapy (20% vs. 25%). This result suggests that surgical treatment may not always be an absolute indication as mentioned in previous studies [5,7]. Our in-hospital case fatality was similar to the results of previous large-scale studies [5,7].

5. Conclusion

Clinicians may encounter non-HACEK Gram-negative infective endocarditis, mostly in medical wards as many intravascular interventions are performed and as elderly patients are managed in those wards.

Disclosure of interest

The authors declare that they have no competing interest.

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