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FREQUENCY OF PRIOR USE OF ANTIMICROBIAL THERAPY AMONG CULTURE-NEGATIVE INFECTIVE ENDOCARDITIS PATIENTS

Avinash[1], Naveedullah Khan[2], Umesh[3], Khalid Bhatti[4], Sunita Bai[5], Shakir Zada[6]

[1,2,3,4,6]*National Institute of Cardiovascular Disease (NICVD), Karachi*
[5,]*Shaheed Mohtarma Benazir Bhutto Medical College (SMBBMC), Lyari*

[1]avinashailani44@gmail.com, [2]drnaveeullah@gmail.com, [3]umeshkumar9099@gmail.com, [4]Khalidsaindad@yahoo.com, [5]hans.sunita@yahoo.com, [6]Dr.shakir637@gmail.com

ABSTRACT

Background: *Culture negative infective endocarditis (BCNIE) is a diagnostic challenge in the setting of a negative standard blood culture. A major contributing factor to this is previous antibiotic usage which can complicate organism identification. If healthcare resources are limited, understanding the prevalence of previous antibiotic exposure in patients with BCNIE is vital for improving diagnostic and treatment time.*

Methodology: *A cross-sectional, hospital-based study, conducted at National Institute of Cardiovascular Diseases (NICVD), Karachi, on 148 patients who fulfilled Duke's Criteria for culture-negative infective endocarditis (BCNIE). Non-probability consecutive sampling of subjects of both sexes aged 20 to 50 years was done. Data were collected from blood cultures and a history of possible previous antibiotic exposure in patient records. Statistical data was analyzed by SPSS version 26.0*

Results: *Out of 148 BCNIE patients, mean ± standard deviation of age was noted as 35.16 ± 10.72, among them 66.9% were female while males were accounted for 33.1%. Prior antibiotic therapy had been administered to 56.1%. Fever (80.4%) and heart murmur (68.2%) were the most prevalent symptoms. Neurological complications (33.8%), heart failure (27.0%) occurred among complications and mortality was 23%.*

Conclusion: *The characteristic of former antibiotic treatment as an independent predictor of culture negativity in infective endocarditis has been demonstrated in this study and applied on over half of patients. These Presenting features include fever and heart murmurs and the complications include acute heart failure and neurological manifestations. These findings highlight the need for careful use of antibiotics as well as appropriate diagnostic tools to promote early diagnosis and treatment of infective endocarditis.*

Keywords: *Antimicrobial therapy, Culture-negative, Infective endocarditis, Duke's criteria*

INTRODUCTION

Timely and oriented identification and management of treatable conditions in patients with infectious cultural negative endocarditis is highly challenging but holds important clinical implications and potential prognostic consequences in terms of end-organ dysfunction due to prior antimicrobials. The negative infectious endocarditis of crop (CNIE) is commonly linked to the previous long antibiotic therapy before definitive organism identification that complicates treatment and may change patients 'results. In specific, the ESC-E-EORP EUDO registry reported much worse effects in sufferers with CNIE unlike positive cultivation situations, prompting tailored healing strategies [1].

The duration and type of previous antimicrobial therapy strongly influence the efficacy of treatment in patients with CNIE. Eichenberger et al. refers to [2] demonstrated that the microbial cell free DNA was helpful in pinpointing up the pathogen which was previously being treated with antibiotics, that would have otherwise darkened the culture results. What that finding could mean is the possibility of a better diagnosis to guide effective treatment in cases where conventional cultures do not succeed. Furthermore, the study by Halavaara et al. and shown that preoperative antimicrobial treatment greatly influences the microbiological results of endocardial samples, thus reinforcing the dangers of the poor peroperative diagnostic picture [3].

In CNIE, the outcome of the patient is significantly tied to the adequacy of the initial management, which is often impacted by a lack of diagnostic information. Results from a multicentric retrospective study demonstrated that experienced hospital mortality rate is significantly higher among patients with CNIE than in patients with positive infectious endocarditis cultivation, mainly due to late diagnosis and suboptimal early management [4]. Buburuz et al. which draw attention to the vitally important aspect of early diagnosis as potential for more favourable clinical outcomes [5] and this statement is supported by Dukes et al., who have identified definite laboratory predictors related to hospital mortality [5].

Several challenges are involved in CNIE diagnosis and are frequently the result of limitations for classical microbiological techniques. Subedi et al. He noted the reliance on the blood cultures can result in an incorrect or delayed diagnosis, particularly when prior antibiotics are given before collection of blood [6]. The administration of more sophisticated diagnostic techniques such as RRNA PCR has proven incremental diagnostic value, possibly steering a more efficient antimicrobial therapy [7]. Still, both the complication of interpretation and the discrepancy in exercise between institutions are fundamental challenges [8].

The practice setting of antimicrobial therapy in CNIE is muddied by local practices out of keeping with guidelines. Tissot-Dupont et al. found that international practices in therapy for antibiotics do not follow recommendations in a uniform way and may help to create the differences found in the results for patients with CNIE [9]. This variability again emphasizes the requirement for standardization in treatment which may improve patient outcomes.

Furthermore, recent perspectives of international studies have recognized contributors to CNIE risks and calls for risk-centric approaches [10]. Together, these findings demand an effort by doctors to arrange standardized protocols this will optimise the determination CNIE and the therapy, actually, to improve results in patients.

Understanding these interaction, the challenges of establishing a diagnosis and the effectiveness of the treatment is instrumental to the understanding of the management of CNIE. Targeted evolutionary treatment guidelines will need to be developed to target the unique issues raised by negative cultivation cases as further studies unravel the novel biology underlying these malignancies, integrated with advanced molecular diagnosis, ultimately making for improved predictions of outcomes for affected patients [11–15].

The forward path requires a multifaceted approach that covers better diagnostic tools, adherence to guidelines and an integral understanding of the implications of previous antimicrobial therapy.

The aim of this study is to evaluate the magnitude of prior use of antimicrobial therapy among culture-negative infective Endocarditis patients. Furthermore, the antimicrobials will be verified in-vitro for their susceptibility pattern against the cultural isolates from the patients of IE at the local level. To the best of knowledge, no such study has been conducted in Pakistan and there is still a gap in knowledge of commonly occurring microorganisms involve in IE and improving outcomes for patients with this complex and heterogeneous disease is still challenging in Pakistan. Moreover, identifying the microorganism and the susceptibility pattern of antimicrobials will help cardiologists or cardiac physicians in knowing and prescribing the appropriate, least toxic as well as economical drugs to their patients of IE. Additionally, in the present era of growing antimicrobial resistance, apposite empirical antimicrobial selection for the treatment of IE is of paramount significance.

METHODOLOGY

The research was conducted in the Department of Cardiology at the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan, employing a descriptive cross-sectional study design. A total of 148 patients, aged 20 to 50 years and of either gender, were enrolled through non-probability, consecutive sampling. Strict inclusion and exclusion criteria were applied to ensure the validity of the results. Patients were

excluded if they had a history of ventricular dysfunction, ventricular tachycardia, bundle branch block on ECG, malignancies such as myeloproliferative disorders, recent surgical interventions, or cardiomyopathies.

Eligible participants were recruited after providing verbal informed consent, during which the purpose, procedures, risks, and benefits of the study were clearly explained. Blood cultures were performed for all participants, and their history of prior antimicrobial use was recorded through interviews and examination of their medical records.

The study focused on infective endocarditis (IE), which is an infection of the endocardial lining of the heart that may involve one or more valves, the septal wall, or the mural endocardium. Cases where no microorganism could be detected using standard blood culture methods were classified as culture-negative infective endocarditis (BCNIE). Endocarditis was identified by the presence of vegetations on cardiac structures as seen on echocardiography. Other findings, such as tissue destruction, abscesses, or ulcerations, also supported the diagnosis.

The Duke's Criteria were used to confirm the diagnosis of infective endocarditis. These criteria require specific combinations of clinical findings for diagnosis: two major and one minor criterion, one major and three minor criteria, or five minor criteria. Major criteria include detecting typical organisms in blood cultures, persistently positive blood cultures over a 12-hour period, or echocardiographic evidence of endocardial involvement, such as oscillating masses or new valvular regurgitation. Minor criteria include factors such as predisposing heart conditions, fever over 38°C, embolic or vasculitic events, immunologic phenomena, or inconclusive blood culture results. The SPSS version 26.0 was used to analyse the collected data. Mean±SD was calculated for quantitative variables. Frequency and percentage were calculated for nominal variables. Chi-square test was applied to evaluate the statistical test of significance at 5% level of significance.

RESULTS

Table 1 outlines the characteristics of the 148 patients diagnosed with culture-negative infective endocarditis (BCNIE). The participants had a mean age of 35.16 ± 10.72 years, with most patients (61.5%) aged between 20–35 years, while 38.5% were older than 35 years.

The mean duration of infective endocarditis was 48.55 ± 30.30 days. Symptoms were reported for 3–50 days in 52.7% of patients, while 47.3% had symptoms lasting longer than 50 days.

In terms of gender, 66.9% of the participants were female, and 33.1% were male.

For clinical presentation, fever was the most common symptom, occurring in 80.4% of patients, followed by heart murmurs in 68.2%. Other clinical features included clubbing (22.3%), splenomegaly (16.9%), anemia (54.7%), thrombocytopenia (9.5%), and leukocytosis (24.3%).

Regarding previous heart disease, rheumatic heart disease was seen in 34.5% of cases, while congenital heart disease and other heart diseases were documented in 26.4% and 29.1%, respectively.

Several complications were identified among the patients. Neurological complications were the most common, affecting 33.8% of participants. Other complications included heart failure (27.0%), peripheral embolism (11.5%), pneumonia (8.8%), and sepsis (7.4%). Less frequent complications included renal failure (6.1%) and hemolysis (4.1%). Mortality was observed in 23.0% of cases (n=34).

Lastly, the data revealed that 56.1% of the patients (n=83) had a history of prior antibiotic use, while 43.9% (n=65) did not report prior antibiotic exposure.

Table II outlines the characteristics of patients with and without mortality among the 148 cases of infective endocarditis.

The mean age of patients who died was 34.53 ± 11.20 years, compared to 35.34 ± 10.61 years for survivors, showing no significant difference (P = 0.700). The duration of infective endocarditis was shorter among those who died (43.15 ± 28.38 days) than survivors (50.16 ± 30.78 days), though this difference was not statistically significant (P = 0.238).

When examining gender, males accounted for a higher proportion of mortality cases (58.8%) compared to females (41.2%), but this association was not statistically significant (P = 0.255).

Regarding clinical presentation, fever occurred in 70.6% of patients who died, compared to 83.3% of survivors (P = 0.100). A heart murmur was noted in 55.9% of patients with mortality and in 71.9% of survivors (P =

0.078). Other symptoms, such as clubbing (32.4% in mortality vs. 19.3% in survivors; P = 0.108), splenomegaly (17.6% vs. 16.7%; P = 0.893), anemia (61.8% vs. 52.6%; P = 0.348), thrombocytopenia (14.7% vs. 7.9%; P = 0.234), and leukocytosis (26.5% vs. 23.7%; P = 0.740), did not show statistically significant differences.

In terms of previous heart disease, rheumatic heart disease was more common among those who died (44.1%) compared to survivors (31.6%) (P = 0.177). Similarly, congenital heart disease was reported in 38.2% of mortality cases versus 22.8% in survivors (P = 0.073), while other heart diseases were noted in 41.2% of mortality cases compared to 25.4% of survivors (P = 0.076).

When analyzing complications, neurological complications were observed in 47.1% of those who died, compared to 29.8% in survivors (P = 0.062). Heart failure showed a significant association with mortality, occurring in 47.1% of patients who died compared to 21.1% of survivors (P = 0.003). Other complications, such as renal failure (5.9% vs. 6.1%; P = 0.659), hemolysis (8.8% vs. 3.6%; P = 0.136), peripheral embolism (17.6% vs. 11.9%; P = 0.199), pneumonia (14.7% vs. 7.0%; P = 0.157), and sepsis (11.8% vs. 6.1%; P = 0.226), were more frequent in mortality cases but did not reach statistical significance.

DISCUSSION

The infectious endocarditis (IE) represents a serious and potentially lethal infection that requires timely diagnosis and aggressive treatment. However, a subset of patients presents negative infectious endocarditis to culture (CNIE), which places significant challenges to doctors [16]. The previous antimicrobial therapy affects the implications and results for these patients, influencing both the diagnostic accuracy and the effectiveness of the treatment.

The previous antimicrobial treatment is often a common factor in patients who present CNIE, complicating the ability to identify the causal body through blood cultures. Failure to identify purification of a pathogen can result in incorrect therapy based on imperfect diagnostic information, as doctors can be reluctant to commence empirical antimicrobial regimes [17]. This scenario is however, complicated by the possibility of patients receiving broad-spectrum antibiotics prior to culture collection, which severely limits the ability to isolate offending microbes [18].

These implications and consequences associated with the antecedent antibiotic therapy in patients with CNIE pose significant hurdles to accurate diagnosis and management. Pre-existing antimicrobial use limits the positive diagnostic utility of blood cultures [19], as patients may already be on broad spectrum IV therapy, which can render positive blood cultures impossible to accomplish, leading to inappropriate therapy initiation and an increased likelihood of adverse events, including mortality or postoperative complications [19]. Hence, it is pivotal for the physician to be cognizant of these pitfalls and utilize the available diagnostic and clinical tools to optimize the therapeutic armamentarium used against patients with infectious endocarditis. Considering that the current studies highlight the need for improvement in the management of CNIE [20], the continuation of the research is justified in order to establish better diagnostic pathways and therapeutic strategies.

In our study, 83 (56.1%) individuals had prior use of antibiotic therapy and 65 (43.9%) individuals did not. In more than half of the cases, antibiotics were already administered before the diagnostic procedure, which may influence culture positivity rates. In a study, 52% of patients previously received antibiotics [21]. A different study also mentioned that 47.1% were placed on antibiotics before the blood draw [22].

A strong aspect of this study is its focus on an important gap in knowledge related to the management of IE, namely, the effect of previous antimicrobial therapy on culture negativity. Such focus offers significant information for clinicians, microbiologists, and policymakers. It is a well-conducted study, with detailed information on the history of the patient including the types and duration of antimicrobial therapy administered, the time to the first diagnosis, and the history of malignant diseases involved. In addition, it underscores the need for diagnostic stewardship and the role of broad diagnostic pathways for patients suspected to have IE.

The importance of this study is further highlighted by the key role it may play in formalizing a clinical practice policy. It highlights the potential harm from empirical antibiotics used when clinical suspicion for IE is

minimal and the consequences of prior antimicrobial therapy, supporting the need for institutional guidelines that promote early diagnostics over treatment.

Despite its assets, the study had a few limitations that should be acknowledged. There are two chief limitations we must address. First, the retrospective nature of the data may allow recall or selection bias, especially with respect to accurate recording of prior antimicrobial use. Information is being relied upon from self-reports by patients regarding their medication history, which could be biased and may change the study results. Another limitation is that the study may be subject to not only variations in access to care, which may be determinants of delays to diagnosis and subsequent antibiotic exposure, but also variations in care once access is established. A significant gap, however, is that these studies did not have any molecular diagnostic methods like polymerase chain reaction (PCR) or next-generation sequencing (NGS) of pathogens. They are used more and more for diagnosis of CNIE as they detect the microbial DNA from the blood or tissue. Such approaches are missing in case reporting, and their absence may neglect the actual microbiological burden of IE.

It did not fully explore how regional factors, such as antimicrobial stewardship practices, may have influenced CNIE rates as well. Because indiscriminate antimicrobial use is rampant in areas with unregulated access to antibiotics, the rates of CNIE may be higher in these regions. These sociocultural and systemic factors need to be probed deeper in future studies.

The results from this study provide several recommendations. First, clinicians must follow their protocols itemizing that blood cultures should be drawn before starting antimicrobial therapy in patients with suspected IE. Early and appropriate diagnostic sampling is critical for accurately identifying pathogens and optimal therapy for all who present with suspected IE.

Secondly health care institutions must encourage antimicrobial stewardship programs (ASPs) to reduce unnecessary antibiotic prescription. These programs must be directed towards training health-care providers to identify the clinical manifestations of IE and to abstain from initiating empirical antibiotics without an adequate clinical assessment.

The third big one is improving diagnostic capabilities. The use of molecular diagnostic techniques such as PCR and NGS combined with classical methods may allow for improved pathogen detection in cases of CNIE. These technologies are expensive today but might save money if they reduce the uncertainty around the diagnosis and the duration of the empirical therapy.

Finally, educating the patients prevents their self medication. Public health program should focus on dissemination of information on the dangers of antibiotic exposed among the population with low accessibility to health facilities.

Prior intravenous antimicrobial therapy is one of the strongest impediments to the precise microbiologic diagnosis of infective endocarditis. Although this study emphasizes the significance of sampling in early diagnostics, its implications extend to the use of empirical antibiotics in clinical practice. Improving antibiotic stewardship, developing new diagnostic technologies, and patients' education would help tackle the shared challenge of this public health burden, CNIE. Future research should be directed towards molecular diagnostics and the socio-economic determinants of antimicrobial use in different populations. This will ultimately enable patients with IE to be treated with the speed, accuracy and effectiveness needed to improve outcomes and lessen the global burden of this complex condition.

CONCLUSION

The characteristic of former antibiotic treatment as an independent predictor of culture negativity in infective endocarditis has been demonstrated in this study and applied on over half of patients. These Presenting features include fever and heart murmurs and the complications include acute heart failure and neurological manifestations. These findings highlight the need for careful use of antibiotics as well as appropriate diagnostic tools to promote early diagnosis and treatment of infective endocarditis.

Table I: Characteristics of Study Participants (n=148)	
Variable	**n (%)**
Age (Mean ± SD) = 35.16 ± 10.72	
20 - 35 years	91 (61.5)
>35 years	57 (38.5)
Duration of Infective Endocarditis (Mean ± SD) = 48.55 ± 30.30	
3 - 50 days	78 (52.7)
>50 days	70 (47.3)
Gender	
Female	99 (66.9)
Male	49 (33.1)
Presentation	
Fever	119 (80.4)
Heart murmur	101 (68.2)
Clubbing	33 (22.3)
Splenomegaly	25 (16.9)
Anemia	81 (54.7)
Thrombocytopenia	14 (9.5)
Leukocytosis	36 (24.3)
Previous Heart Disease	
Rheumatic Heart Disease	51 (34.5)
Congenital Heart Disease	39 (26.4)
Other Heart Disease	43 (29.1)
Complications	
Neurological complications	50 (33.8)
Renal failure	9 (6.1)
Hemolysis	6 (4.1)
Peripheral embolism	17 (11.5)
Pneumonia	13 (8.8)
Heart failure	40 (27.0)
Sepsis	11 (7.4)
Mortality	34 (23.0)
Prior Use of Antibiotic Therapy	
Yes	83 (56.1)
No	65 (43.9)

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Pneumonia	13 (8.8)
Heart failure	40 (27.0)
Sepsis	11 (7.4)
Mortality	34 (23.0)
Prior Use of Antibiotic Therapy	
Yes	83 (56.1)
No	65 (43.9)

Table II: Characteristics of Patients with Mortality (n=148)

Variables		Yes (n=34)	No (n=114)	95% C. I	P-Value
Age in years, Mean ± SD		34.53 ± 11.20	35.34 ± 10.61	-4.966----3.341	0.700
Duration of IE in days, Mean ± SD		43.15 ± 28.38	50.16 ± 30.78	-18.697----4.675	0.238
Gender	Male, *n* (%)	20 (58.8)	79 (69.3)	(0.287----1.395)	0.255
	Female, *n* (%)	14 (41.2)	35 (30.7)		
Presentation	Fever, *n* (%)	24 (70.6)	95 (83.3)	(0.198----1.165)	0.100
	Heart murmur, *n* (%)	19 (55.9)	82 (71.9)	(0.224----1.090)	0.078
	Clubbing, *n* (%)	11 (32.4)	22 (19.3)	(0.850----4.707)	0.108
	Splenomegaly, *n* (%)	6 (17.6)	19 (16.7)	(0.390----2.942)	0.893
	Anemia, *n* (%)	21 (61.8)	60 (52.6)	(0.664----3.182)	0.348
	Thrombocytopenia, *n* (%)	5 (14.7)	9 (7.9)	(0.626----6.468)	0.234
	Leukocytosis, *n* (%)	9 (26.5)	27 (23.7)	(0.483----2.785)	0.740
Previous Heart Disease	Rheumatic Heart Disease, *n* (%)	15 (44.1)	36 (31.6)	(0.781----3.745)	0.177
	Congenital Heart Disease, *n* (%)	13 (38.2)	26 (22.8)	(0.924----4.750)	0.073
	Other Heart Disease, *n* (%)	14 (41.2)	29 (25.4)	(0.920----4.578)	0.076
Complications	Neurological complications, *n* (%)	16 (47.1)	34 (29.8)	(0.955----4.580)	0.062
	Renal failure, *n* (%)	2 (5.9)	7 (6.1)	(0.189----4.829)	0.659
	Hemolysis, *n* (%)	3 (8.8)	3 (2.6)	(0.688----18.627)	0.134
	Peripheral embolism, *n* (%)	6 (17.6)	11 (9.6)	(0.682----5.902)	0.199
	Pneumonia, *n* (%)	5 (14.7)	8 (7.0)	(0.695----7.513)	0.165
	Heart failure, *n* (%)	16 (47.1)	24 (21.1)	(1.483----7.494)	0.003
	Sepsis, *n* (%)	4 (11.8)	7 (6.1)	(0.559----7.430)	0.226

IE: Infective Endocarditis

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