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Polymicrobial Infective Endocarditis: Clinical Features and Prognosis

Pablo Elpidio García-Granja, MD, Javier López, MD, PhD, Isidre Vilacosta, MD, PhD, Carlos Ortiz-Bautista, MD, Teresa Sevilla, MD, PhD, Carmen Olmos, MD, PhD, Cristina Sarriá, MD, PhD, Carlos Ferrera, MD, Itziar Gómez, BS, and José Alberto San Román, MD, PhD

Abstract: To describe the profile of left-sided polymicrobial endocarditis (PE) and to compare it with monomicrobial endocarditis (ME).

Among 1011 episodes of left-sided endocarditis consecutively diagnosed in 3 tertiary centers, between January 1, 1996 and December 31, 2014, 60 were polymicrobial (5.9%), 821 monomicrobial (81.7%), and in 123 no microorganism was detected (12.2%). Seven patients (0.7%) were excluded from the analysis because contamination of biologic tissue could not be discarded. The authors described the clinical, microbiologic, echocardiographic, and outcome of patients with PE and compared it with ME.

Mean age was 64 years SD 16 years, 67% were men and 30% nosocomial. Diabetes mellitus (35%) were the most frequent comorbidities, fever (67%) and heart failure (43%) the most common symptoms at admission. Prosthetic valves (50%) were the most frequent infection location and coagulase-negative *Staphylococci* (48%) and enterococci (37%) the leading etiologies. The most repeated combination was coagulase-negative *Staphylococci* with *enterococci* (n = 9). Polymicrobial endocarditis appeared more frequently in patients with underlying disease (70% versus 56%, $P = 0.036$), mostly diabetics (35% versus 24%, $P = 0.044$) with previous cardiac surgery (15% versus 8% $P = 0.049$) and prosthetic valves (50% versus 37%, $P = 0.038$). Coagulase-negative *Staphylococci, enterococci,* Gram-negative bacilli, anaerobes, and fungi were more frequent in PE. No differences on age, sex, symptoms, need of surgery, and in-hospital mortality were detected.

Polymicrobial endocarditis represents 5.9% of episodes of left-sided endocarditis in our series. Despite relevant demographic and microbiologic differences between PE and ME, short-term outcome is similar.

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Abbreviations: HIV = human immunodeficiency virus, IE = infective endocarditis, ME = monomicrobial endocarditis, PE = polymicrobial endocarditis.

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From the Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario, Valladolid (PEG-G, JL, CO-B, T S, IG, JASR); Hospital Clínico Universitario San Carlos (IV, CO, CF); and Hospital Clínico Universitario la Princesa, Madrid, España (CS).
Correspondence: Pablo Elpidio García-Granja, MD, Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario, C/ Ramón y Cajal 3, 47005 Valladolid, España (e-mail: pabloelpidio88@gmail.com).
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INTRODUCTION

Nowadays, the causative microorganism is identified in roughly 90% of the episodes of infectious endocarditis (IE).[1] The isolation of more than one microorganism in patients with IE is quite uncommon, ranging from 1% to 6.8%.[2,3]

Theoretically, polymicrobial infective diseases are associated with a worse clinical course and prognosis than monomicrobial diseases.[4–6] In the case of IE, this hypothesis remains unsettled, because scanty information is available in the literature. Besides, no comparison between polymicrobial endocarditis (PE) and monomicrobial endocarditis (ME) has been undertaken.

Our purpose has been to analyze the clinical, microbiologic, and echocardiographic profile and the outcomes of patients with left-sided PE. We also aimed to compare them with that of patients with ME to establish whether the isolation of more than one pathogen is related to worse prognosis.

METHODS

Study Population

Since January 1, 1996 to December 31, 2014, all patients with a final diagnosis of IE admitted in three tertiary centers were included in an ongoing multipurpose database. We used the Duke criteria until 2002[7] and the modified Duke criteria[8] thereafter. All participant hospitals followed a standardized protocol, in which every patient underwent at least 1 physical examination, electrocardiogram, blood analysis, urine analysis, set of 3 blood cultures, and transthoracic and transesophageal echocardiography. We filled a standardized case report form with 26 epidemiological, 72 clinical, 26 laboratory, 6 electrocardiographic, 27 microbiologic, and 68 echocardiographic variables for every patient. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethical committees.

To establish the causative microorganism of each episode of IE, we combined both the information of the blood cultures and that obtained from the cultures of biologic infective tissues (ie, explanted valves or prosthesis, embolic material, etc). Patients were divided into 3 groups depending on the number of causative microorganims: PE (2 or more microorganims); ME (one); and unknown microorganism (zero). Patients in whom coagulase-negative *Staphylococci* or other common skin contaminants grew up in the cultures of a biologic infected tissue and not in the blood cultures were excluded from the analysis because contamination could not be ruled out. The main characteristics of PE were compared with those of ME.

Definition of Terms

The episode of endocarditis was considered polymicrobial when 2 or more microorganims were cultured in at least 3 blood samples or isolated from infected tissues simultaneously or

consecutively within 7 days of the initial positive blood culture without evidence of other clinical infectious foci. Antibiotic treatment and indications of surgery followed the recommendations of the current European guidelines in every moment throughout the study period. Urgent surgery was defined as that performed before the finalization of the antibiotic treatment. If the signs and symptoms of the IE started after 48 hours from the hospital admission or in the first 3 days after discharge or up to 30 days after an operation, the episode was considered as nosocomial. We have analyzed possible predisposing events as situations with theoretical risk of bacteremia occurring within the previous 2 months of the beginning of the disease. Chronic renal disease was defined as a decrease of glomerular filtration rate below 60 ml/min/1.73 m^2 for at least 3 months. Early prosthetic valve endocarditis was defined as occurring less than 1 year after surgery.[9] Other definitions used in this study have been already described in previous works.[10]

Statistics

Categorical variables are reported as frequency (n) and percentages. Continuous variables as mean ± standard deviation or median and interquartile range (IQR). Normal distribution of quantitative variables was verified with the Kolmogorov–Smirnov test. Qualitative variables were compared with the χ^2 test and Fisher exact test. Continuous variables were compared with Student *t* test or its equivalent for nonparametric tests, Mann–Whitney *U* test, for variables that were not normally distributed. Data were analyzed using the SPSS V 15.0 software package (SPSS, Chicago, IL).

RESULTS

Epidemiological Features of Polymicrobial Endocarditis

From January 1, 1996 to December 31, 2014, 1195 episodes of definite IE were diagnosed. Of them, 1011 were left-sided (85%) and formed our study group: 60 were polymicrobial (5.9%), 821 monomicrobial (81.2%), and in 123 patients no microorganism was detected (12.1%). Seven patients (0.7%) were excluded from the analysis because contamination of biologic tissue could not be discarded.

Mean age was 64 years, SD 16 years (IQR: 57–75) and 40 were men (67%). The infection was nosocomial in 18 patients (30%). Of the remaining 42, 34 episodes were community acquired (57%) and 8 healthcare associated (13%). There were 53 patients with previous known cardiac abnormalities (90%): 30 (50%) had prosthetic valves, 12 (20%) degenerative, 5 (8%) rheumatic valvular heart disease, 2 (3%) congenital abnormalities, and 4 (7%) left-ventricular hypertrophy. Previous IE had occurred in 5 patients (8%).

The spectrum of predisposing conditions was as follows: 10 (17%) indwelling intravenous catheters, 9 (15%) previous cardiac surgery, 7 (12%) local infections, 4 (7%) urogenital manipulations, and 3 (5%) dental manipulations. Only 1 patient was intravenous drug user. Finally, 42 patients (70%) had underlying conditions, being diabetes mellitus (35%), and chronic renal failure (17%) the most frequent. Just 1 patient was HIV positive.

Clinical and Echocardiographic Profile of Polymicrobial Endocarditis

Time of evolution of symptoms to diagnosis was 46 days (IQR 7–61). The most frequent initial symptoms at admission were fever (n = 40; 67%), dyspnea (n = 27; 48%), and shivering (n = 23; 41%). During hospitalization 60% developed heart failure, 45% renal failure, 28% persistent infection, 20% stroke, and 13% cardiogenic shock.

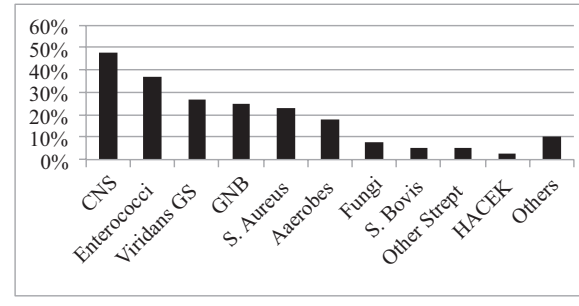
Polymicrobial endocarditis affected native valves in 30 patients (19 mitral, 16 aortic) and prostheses in 30 (16 mechanical mitral prostheses, 8 mechanical aortic, 5 aortic bioprostheses, and 3 mitral bioprostheses). Early-onset prosthetic valve endocarditis occurred in 11 patients (37%) and late onset in 19 patients (63%). There were 12 multivalvular episodes. Transesophageal echocardiograms revealed valvular vegetations in 48 patients (80%) (diameter $18.4 \pm 35 \times 7.3 \pm 4.1$ mm; area 0.40 ± 0.6 cm^2), at least one periannular complication in 13 (22%) (5 abscesses, 8 pseudoaneurysms, and 2 fistulas), and moderate or severe valvular regurgitation in 40 (67%).

Microbiologic Profile of Polymicrobial Endocarditis

The diagnosis of PE was performed according to the results of blood cultures or serology in 36 patients (60%), with cultures of biologic infected tissues in 7 (12%) and with the combination of both in 17 (28%). Three microorganisms were isolated in 6 patients and 2 in the rest. Coagulase-negative *staphylococci,* enterococci, Gram-negative bacilli and *Staphylococcus aureus* were the predominant pathogens. The microbiologic profile of PE is represented in Figure 1. The most frequent combinations of microorganims were: coagulase-negative *Staphylococci* plus enterococci (n = 9, 15%), coagulase-negative *Staphylococci* plus Gram-negative bacilli (n = 5, 8%) and coagulase-negative *Staphylococci* plus *Streptococcus viridans* (n = 5, 8%). A total of 60% of staphylococcal strains were methicillin resistant and there were no streptococcocal strains resistant to penicillin.

Treatment and Outcome of Polymicrobial Endocarditis

Surgery was performed in 39 patients (65%): urgent in 19 (49%) and elective in 20 (51%). The main indications for urgent surgery were severe valvular dysfunction (45%), heart failure (42%) and persistent infection (42%). Patients received 3.1 ± 0.8 antibiotics for a median of 10 ± 5.7 weeks. Distribution of antibiotics was as follows: glycopeptides (65%), aminoglycosides (60%), penicillins (53%), cephalosporins (25%), carbapenems (10%), and fluoroquinolones (8%). Hospital stay was 49 ± 30 days and total in-hospital mortality 33% (n = 20). Principal causes of death were: uncontrolled infection (25%), heart failure (20%), and hemodynamic instability during extracorporeal circulation (20%).



CNS = coagulase negative *Staphylococci,* GNB = Gram-negative bacilli, S. aureus = *Staphylococus aureus,* Viridans GS = *Viridans group streptococci.*

FIGURE 1. Microbiologic profile of the 60 episodes of polymicrobial left-sided infective endocarditis.

TABLE 1. Demographic, Clinical, Echocardiographic and Outcome Differences Between Polymicrobial and Monomicrobial Endocarditis

	PE (n = 60)	ME (n = 821)	*P*
Mean age, years; mean ± SD	64 ± 16	64 ± 14	0.132
Men, n (%)	40 (67)	529 (64)	0.727
Origin			
Nosocomial, n (%)	18 (30)	215 (26)	0.518
Not nosocomial	42 (70)	606 (74)	
Community acquired, n (%)	34 (81)	554 (91)	0.046
Healthcare related, n (%)	8 (19)	52 (9)	
Previous Heart Disease			
Rheumatic valve disease, n (%)	5 (8)	84 (10)	0.638
Pre-existing prosthetic valve, n (%)	30 (50)	302 (37)	0.041
Degenerative valve disease, n (%)	12 (20)	143 (17)	0.612
Previous endocarditis, n (%)	5 (8)	51 (6)	0.579
Congenital heart disease, n (%)	2 (3)	34 (4)	0.999
Predisposing Events			
Local infection, n (%)	7 (12)	97 (12)	0.973
Intravenous catheters, n (%)	10 (17)	110 (13)	0.476
Dental manipulation, n (%)	3 (5)	47 (6)	0.999
Urogenital manipulation, n (%)*	4 (7)	27 (3)	0.154
Previous cardiac surgery, n (%)†	9 (15)	62 (8)	0.049
Previous noncardiac surgery, n (%)	3 (5)	49 (6)	0.999
Intravenous drug use, n (%)	1 (2)	25 (3)	0.999
Underlying disease	42 (70)	461 (56)	0.036
Diabetes mellitus, n (%)	21 (35)	192 (24)	0.044
Chronic renal insufficiency, n (%)	10 (17)	112 (14)	0.485
Cancer, n (%)	7 (12)	86 (11)	0.774
HIV‡, n (%)	1 (2)	16 (2)	0.999
Symptoms at Admission			
Time symptoms to diagnosis, days, median (IQR)	46 (7–61)	37 (5–40)	0.427
New murmur, n (%)	29 (50)	371 (46)	0.547
Shivering, n (%)	23 (41)	325 (42)	0.843
Fever, n (%)	40 (67)	591 (73)	0.307
Dyspnea, n (%)	27 (48)	331 (41)	0.301
Heart failure, n (%)	26 (43)	324 (40)	0.575
Renal insufficiency, n (%)	8 (14)	157 (19)	0.309
Septic shock, n (%)	1 (2)	58 (7)	0.172
Stroke, n (%)	9 (15)	93 (11)	0.401
Cutaneous manifestations	5 (9)	82 (10)	0.370
Symptoms During Hospitalization			
Fever, n (%)	47 (78)	695 (85)	0.156
Heart failure, n (%)	36 (60)	480 (59)	0.858
Renal insufficiency, n (%)	27 (45)	336 (41)	0.562
Cardiogenic shock, n (%)	8 (13)	134 (16)	0.531
Septic shock, n (%)	4 (9)	106 (19)	0.106
Persistent infection, n (%)	12 (28)	168 (31)	0.723
Stroke, n (%)	12 (20)	145 (18)	0.664
Location			
Native, n (%)	30 (50)	521 (64)	0.038
Mitral, n (%)	19 (32)	336 (41)	0.158
Aortic, n (%)	16 (27)	303 (37)	0.111
Prosthetic, n (%)	30 (50)	300 (37)	0.038
Mechanic mitral, n (%)	16 (27)	155 (19)	0.141
Mechanic aortic, n (%)	8 (13)	99 (12)	0.770
Mitral bioprosthesis, n (%)	3 (5)	12 (2)	0.076
Aortic bioprosthesis, n (%)	5 (8)	70 (9)	0.959
Early onset, n (%)	11 (37)	105 (35)	0.876
Late onset, n (%)	19 (63)	193 (65)	
Multivalvular	12 (20)	191 (23)	0.562
Echo Findings			

	PE (n = 60)	ME (n = 821)	P
Vegetations, n (%)	48 (80)	723 (88)	0.055
Periannular extension, n (%)	13 (22)	231 (28)	0.273
Abscesses, n (%)	5 (8)	130 (16)	0.117
Pseudoaneurysms, n (%)	8 (13)	129 (16)	0.616
Fistulas, n (%)	2 (3)	30 (4)	0.999
Moderate-severe valvular regurgitation, n (%)	40 (67)	573 (70)	0.582
Antibiotic Treatment			
Number of antibiotics, mean ± SD	3.1 ± 0.8	2.7 ± 1	0.002
Duration of treatment, weeks, mean ± SD	10 ± 6	9 ± 7	0.178
Penicillins, n (%)	32 (53)	428 (52)	0.857
Cephalosporins, n (%)	15 (25)	218 (27)	0.792
Carbapenems, n (%)	6 (10)	69 (8)	0.669
Glycopeptides, n (%)	39 (65)	378 (46)	0.005
Macrolides, n (%)	0 (0)	8 (1)	0.999
Aminoglycosides, n (%)	48 (60)	590 (72)	0.581
Fluoroquinolones, n (%)	5 (8)	33 (4)	0.174
Outcome			
Need of surgery, n (%)	39 (65)	487 (59)	0.392
Urgent, n (%)	19 (49)	270 (55)	0.417
Elective, n (%)	20 (51)	217 (45)	
In hospital mortality, n (%)	20 (33)	244 (30)	0.611

[*] Urogenital manipulation: transurethral prostate resections (n = 2), endoscopic lithotripsy (n = 1), cystoscopy (n = 1).
[†] Local infections: chronic infections of the sternotomy (n = 4), infections of the pacemaker?s bag (n = 2), persistent cutaneous infection after removing a chemotherapy catheter (n = 1).
[‡] HIV = human immunodeficiency virus.

Comparison Between Polymicrobial and Monomicrobial Endocarditis

Demographic, clinical, echocardiographic, and outcome differences between PE and ME are depicted in Table 1. Polymicrobial endocarditis appeared more frequently in patients with underlying diseases (70% versus 56%, $P = 0.04$), more often in diabetics (35% versus 24%, $P = 0.04$). It was more frequently prosthetic (50% versus 37%, $P = 0.04$), and healthcare related (19% versus 9%, $P = 0.046$). No differences in other echocardiographic findings were found. Coagulase-negative *Staphylococci,* enterococci, Gram-negative bacilli, anaerobes, and fungi were more frequent in PE (Table 2). Among *Staphylococcal* species, methicillin resistance was more frequent (60% versus 39%, $P = 0.028$) in PE. The number of antibiotics prescribed (3.1 ± 0.8 versus 2.7 ± 1, $P = 0.002$) and the use of glycopeptides (65% versus 46%, $P = 0.005$) were also higher in PE, but the

TABLE 2. Comparison of the Microbiologic Profile Between Polymicrobial and Monomicrobial Endocarditis

	PE	ME	P
Number of microorganisms	126	821	
Coagulase-negative *Staphylococci*, n (%)	29 (48)	166 (20)	<0.001
Enterococci, n (%)	22 (37)	109 (13)	<0.001
[*]Gram-negative bacilli, n (%)	15 (25)	35 (4)	<0.001
Viridans group *streptococci*, n (%)	16 (27)	131 (16)	0.032
Staphylococcus aureus, n (%)	14 (23)	187 (23)	0.921
[†]Anaerobes, n (%)	11 (18)	19 (2)	<0.001
Fungi, n (%)	5 (8)	16 (2)	0.011
Other *Streptococci*, n (%)	3 (5)	67 (8)	0.618
Streptococcus bovis, n (%)	3 (5)	49 (6)	0.999
HACEK, n (%)	2 (3)	5 (1)	0.336
[‡]Others, n (%)	6 (10)	37 (5)	0.065
Methicillin resistant *Staphylococcal* spp, n (%)	18 (60)	131 (39)	0.028
Penicillin resistant *Streptococcal* spp, n (%)	0 (0)	2 (3)	0.999

[*] Gram-negative bacilli: Serratia spp, *Escherichia coli*, *Stenotrophomonas maltophila*, *Enterobacter cloacae*, *Pseudomonas aureginosa*, *Klebsiella pneumoniae*, Acinetobacter spp.
[†] Anaerobes: Corynebacterium spp, Prevotella spp, Propionibacterium spp, Cellulomonas spp, Lactobacilus spp.
[‡] Others: *Lysteria monocytogenes*, Bacillus spp, Micrococcus spp, Leuconostoc spp, *Coxiella burnetti*, and *Chlamydia pneumoniae*.

duration of the antibiotic treatment was similar. No differences in the need of surgery (65% versus 59%, $P = 0.39$) and mortality (33% versus 30%, $P = 0.61$) were observed.

DISCUSSION

Polymicrobial diseases, which are recognized with increasing frequency, are acute and chronic diseases caused by various combinations of viruses, bacteria, fungi, and parasites.[11] It is known that the presence of 1 microorganism can generate a niche for other pathogenic microorganisms to colonise.[12,13] In the particular case of PE, scanty data is available, only case reports,[11,14,15] small series[16–18] and a systematic review in 1991[19] have been reported.

Our investigation, to our knowledge, is the first prospectively recruited series, which depicts the current characteristics of PE, and compares them with those of ME. Our results shed light on this topic, which has been systematically left out when IE has been analyzed.

Some important consequences can be drawn from the investigation herein presented: prevalence of PE in our series is higher than previously reported; coagulase-negative *Staphylococci, enterococci,* Gram-negative bacilli, anaerobes, and fungi are more frequently encountered as causative pathogens in PE; staphylococcal strains were more frequently methicillin resistant in PE; but in spite of all these differences, the clinical profile and the prognosis are very similar. Any of these findings deserves a comment.

Epidemiology and incidence of PE has not been determined. In older studies, PE affects predominantly drug abusers and patients with valvular prosthesis,[15–24] and the incidence was reported ranging from 1% in unselected populations to 6.8% in drug users,[2,3] although nowadays it could be higher.[18] Our work shows an incidence of 5.9% and only 1 patient was drug addict. This difference with previous older studies can be explained by 3 facts. First, the definition of PE used in our study. We not only considered the results of the blood cultures, but also the cultures of infected tissues related to the endocarditis, for example the valves, prosthesis or embolic material explanted during surgery. In fact, in 40% of our PE patients the diagnosis was performed taking into account these cultures. Other explanation might be the progressive improvement in the microbiologic techniques, which have incremented the sensitivity to detect microorganisms.[25–27] Lastly, we have excluded right-sided endocarditis from our study. Our incidence would have been higher (6.6%) if 7 patients with coagulase-negative *Staphylococci* in the cultures of biologic material had been included, but as the possibility of contamination could not be ruled out, we decided to exclude them from the analysis.

Several reasons are behind the microbiologic profile of PE in our series. The high proportion of prosthetic episodes, the frequent association with underlying diseases, as diabetes mellitus, or the association with healthcare exposure can explain that coagulase-negative *Staphylococci* are the leading cause of PE, and the high proportion of methicillin resistant staphylococcal strains. In fact, they are the most common microorganisms isolated in early-onset prosthetic valve IE[28] but also in blood cultures as result of contamination.[29] Taking into account this last consideration, we only considered them as etiologic agents of the episode of IE when they were isolated in three consecutive blood cultures, excluding those cases with only isolation in biologic infected tissues. Enterococci, which are reportedly the third most common group of IE-causing pathogens,[30] are the second main etiology of PE. They share with *staphylococci* a high capacity of adhering to the endocardium, fibrin, and platelets.[31–37] Theoretically, synergy between these microorganisms may also favor the infective pattern herein found. Nevertheless, there is little clinical evidence that synergy is important to the pathogenesis of IE. It is noteworthy that anaerobes were cultured in almost 20% of PE, whereas in ME their prevalence was anecdotal. It is well known that polymicrobial infections usually involve anaerobes,[38] and many mechanisms explaining this synergy have been proposed; inhibition phagocytosis of aerobes by leukocytes, provision of essential nutrients, such as vitamin K, succinate, and various growth factors, alteration of local environment, including reduction of the oxygen tension and lowering of redox potential and provision of substances toxic to the host that permit species of bacteria to flourish concurrently.

Finally, it has to be emphasized that clinical characteristics of PE did not differ substantially from ME and more importantly, the presence of more than one pathogen in cultures does not adversely affect prognosis. A small retrospective investigation had already suggested a similar outcome of both groups of patients.[39] In this regard, a recent prospective study in critically ill patients at an intensive coronary care unit further supports our results[40] no differences in mortality were seen between 75 patients with polymicrobial bloodstream infection and 371 with monomicrobial. Therefore, from a practical standpoint, the management and the therapeutic strategy of patients with IE should be the same irrespective of whether the patient has PE or ME.

In conclusion, incidence of left-sided PE is higher than previously reported. Despite PE has a specific epidemiologic and microbiologic profile, its clinical course and prognosis are similar to that of ME.

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