AIDS Reviews 2004;6:97-106

Endocarditis in the Setting of HIV Infection

M.ª Eulalia Valencia[1] and José M.ª Miró[2]

[1]Infectious Diseases Service, Hospital Carlos III, Madrid, Spain. [2]Infectious Diseases Service, IDIBAPS, Hospital Clínic, University of Barcelona, Barcelona, Spain

Abstract

Background: ***Cardiac complications are becoming more important in patients with HIV infection. The most common is infective endocarditis (IE) in patients who are intravenous drug addicts (IVDA). Other less common problems are pulmonary hypertension, cardiotoxicity, pericardial effusion, cardiac neoplasms, etc.***

Patients and methods: ***A literature review of published studies on IE was done and the personal experience of the authors is reflected.***

Results: ***The clinical pattern of IE has remained unchanged. It is usually due to*** **Staphylococcus aureus** ***and is more commonly localized to the right side of the heart. It is not clearly defined if HIV infection is responsible for the worst evolution in these patients and the treatment is the same as that used in HIV– subjects.***

Conclusions: ***IE is responsible for 5-20% of hospital admissions and for 5-10% of total deaths in IVDA patients with HIV infection, but the clinical outcome of the patients depends on the affected valve and the culture germen rather than the HIV serostatus.*** **(AIDS Reviews 2004;6:97-106)**

Key words

Infective endocarditis. HIV. HAART. **Staphylococcus aureus.**

Introduction

The introduction of highly active antiretroviral therapy (HAART) regimens has substantially increased the survival in patients infected with the HIV (HIV)[1-3]. Consequently, previously uncommon manifestations such as cardiac complications are becoming more frequent. In general, cardiac manifestations in patients with HIV infection are clinically subtle in their initial stages. Symptoms are usually non-specific; however, dyspnea is very common and may be overlooked or attributed to pulmonary diseases and opportunistic infections. Cardiac abnormalities in HIV infection may involve any of the structures of the heart, including pericardium, myocardium and endocardium[4]. Furthermore, HIV infection is associated with pulmonary hypertension, cardiac neoplasms, and the use of potentially cardiotoxic medications[5-10]. In the case of infective endocarditis (IE) this situation is different because their prevalence in HIV-infected patients is similar to that in subjects of other risk groups, such as intravenous drug addicts (IVDA). However, in regard to this disease it is possible to distinguish three different frequency patterns: 1) HIV-infected patients have the same incidence of IE as that observed in the general population, but less than IVDAs; 2) IVDA patients with HIV infection a have greater incidence of IE than IVDAs without HIV infection, and 3) HIV-infected subjects treated with HAART have a significant decrease in incidence when compared with a similar group before HAART use[11,12].

The term "infective endocarditis" describes the infection of the endocardial surface of the heart and implies the physical presence of microorganisms in the lesion. The heart valves are most commonly affected, but the dis-

Correspondence to:
M.ª Eulalia Valencia
Service of Infectious Diseases
Hospital Carlos III
Sinesio Delgado, 10
28029 Madrid, Spain
Phone: +34 91 4532500
Fax: +34 91 7336614
E-mail: evalencia.hciii@salud.madrid.org

ease may also occur on septal defects or in the mural endocardium. Estimates of endocarditis prevalence vary from 6.3 to 34% of HIV-infected patients who use intravenous drugs, independent of HAART regimens[13-15]. It is a very unusual condition in other groups of patients at risk for HIV infection and similar, in regard to etiologic agent and clinical manifestations, to the general population with similar sex and age. Losa, et al.[16] published eight cases between 1979 and 1999 and reviewed the literature, concluding that a wide etiologic range is found, reflecting different clinical and environmental conditions, and that it is developed in patients with advanced HIV disease. However, the prognosis is not worse than in HIV– patients with IE.

Infective endocarditis in IVDAs appears by the repetitive bombardment with injected substances and microorganisms in patients with immunological abnormalities and immunosuppression due to intravenous (i.v.) drug use and HIV. It is responsible for 5-20% of hospital admissions and for 5-10% of total deaths. IVDAs often have recurrent endocarditis. Since the first descriptions, the clinical pattern has remained unchanged. It is usually due to *Staphylococcus aureus* and is more commonly localized to the right side of the heart. Nevertheless, mixed or left-sided valvular infections are also frequent[11,12,17,18]. In recent years the incidence may be decreasing, probably due to changes in injection practices (such as less use of the parenteral route or increased use of sterile needles and syringes) undertaken to avoid HIV transmission[19,20]. However, it is very important to remark that the incidence of IE is related to i.v. drug use and, although the use of illegal drugs is actually decreasing in Europe and the USA, this is still a very important problem in east-European countries and Asia. For this reason, IE will probably be a serious health problem in these countries and consequently in ours due to immigration from the abovementioned nations.

In general, IE is reported in the early stages of HIV infection and the impact of its presence and related degree of immunosuppression has not been defined completely. However, Manoff, et al.[21] found in 1996 that HIV-related immunodeficiency may independently increase the risk of IE among IVDAs.

Causative organisms of infective endocarditis

A remarkable range of microbial species can cause IE, but most cases are due to the common gram positive cocci independent of HIV serostatus[12,15,22]. The blood cultures are positive in 70-90% of cases and *Staphylococcus aureus* is the most common etiological agent in all series. More than 95% of strains, acquired either in the community or in hospital, elaborate beta-lactamase and therefore are resistant to penicillin, but in most geographical areas they are sensitive to methicillin (MSSA)[12,17,23]. The other frequently isolated agents are streptococci, enterococci (15-20%), *Pseudomonas aeruginosa*, *Serratia marcescens* and other gram negative bacilli (<10%) and *Candida* spp. (<2%). Less common or rare etiologic organisms include *Pseudomonas* spp., *Xanthomonas maltophilia, Neisseria* spp., coagulase-negative staphylococci, *Erysipelothrix* spp., *Gemella morbillorum, Citrobacter* spp., *Haemophilus* spp. and *Einekella corrodens*[24-27]. *Staphylococcus aureus* probably originates from the drug user's own skin, while other bacteria and fungi may be found in the drugs themselves, adulterants, or contamination of the injection equipment or the diluents[18].

Negative blood cultures are present to a variable percentage in different series: Ribera, et al.[15] found only 3.7% in HIV+ patients and 4.5% in those HIV–, Cicalini, et al. found 13% (all patients had HIV infection) and Valencia, et al.[17] has the most elevated rate of negative blood culture with 36% in HIV-infected patients and 21% in subjects without HIV. Although it is not analyzed, the authors speculate that the use of cotrimoxazole or another type of antibiotic prophylaxis in patients with advanced HIV infection could explain this elevated rate of negative blood culture.

Polymicrobial endocarditis is uncommon and may occur in 2-6% of cases. Among 201 cases of IE, Valencia, et al.[29] found 12 patients (6%) with polymicrobial endocarditis. The most common combinations of organisms were *S. aureus* with *S. pneumoniae* and *S. aureus* with *Pseudomonas aeruginosa.*

In patients with HIV but not IVDAs, the agents isolated in the blood cultures are very different and a wide etiological range is found, reflecting different clinical and environmental conditions. Losa, et al.[16] studied eight cases and IE was caused by *Enterococcus faecalis* in three cases, staphylococci in two and *Salmonella enteritidis*, *viridans* group streptococci and *Coxiella burnetii* in one case each.

Table 1 compares the etiology in three Spanish publications about IVDA patients with IE. The most common microorganisms have been selected.

Echocardiography and valvular involvement

Soon after its introduction into clinical practice, echocardiography proved useful in evaluating the condi-

Table 1. Etiology of infective endocarditis in intravenous drug addicts: analysis of three Spanish publications. In two of them HIV+ and HIV– patients are differentiated

	Miró, et al. Etiology of IE in IVDAs: analysis of 1529 episodes diagnosed in Spain (1977-1993). Combined HIV+ and HIV–	Ribera, et al. Results of bacteriology in 283 episodes of IE in IVDAs		Valencia, et al. Results of blood cultures in 164 episodes of IE in IVDAs	
		HIV+ (n = 216)	HIV– (n = 67)	HIV + (n = 143)	HIV– (n = 21)
Staphylococcus aureus	1138 (74%)	159 (73.6%)	38 (56.7%)	68 (48%)	12 (63%)
Streptococcus viridans	94 (6%)	24 (11.1%)	20 (29.8%)	7 (5%)	–
Polymicrobial	44 (3%)	11 (5.1%)	1 (1.5%)	7 (5%)	1 (5%)
Negative cultures	106 (7%)	8 (3.7%)	3 (4.5%)	52 (36%)	4 (21%)

tions of patients suspected of having IE. Their sensitivity for valvular abnormalities associated with IE is more than 95% and false-positive findings are rare and irrespective of HIV serostatus. Echocardiography detects the vegetation location and size and it is useful for diagnosing cardiac dysfunction. Regurgitation may be observed in 9-45% of cases, pericardial effusion in 5% and ventricular dysfunction in 3-5%[5,30,31].

Right-sided valves are predominantly affected because most patients are IVDAs. In all series, the tricuspid is the most frequently damaged valve (50-90%), followed by the mitral and aortic valves (8-30%). Pulmonic valve infection is rare, but some isolated cases have been published. Sometimes more than one valve with endocarditis is detected simultaneously (5-18%)[15,17,18,22,28,32]. It is not definitively known why the tricuspid valve is the principal location of IE in IVDAs. One hypothesis is that the endothelial damage is caused by physical bombardment of the tricuspid valve by impurities contained in injected drugs or adulterants[33].

Left-sided endocarditis has special clinical, epidemiological and microbiological characteristics, its relationship with HIV+ IVDAs is unknown, and it is more common in HIV– subjects. In a study of 34 cases, it was observed that 30 patients had been IVDAs but only 18 were active IVDAs. The affected valve was mitral in 31 patients (91%) and blood cultures were negative in 21 episodes (62%)[15,18,28,34].

In HIV-infected patients with IE not related to intravenous drug abuse, the mitral and aortic valves are those most frequently affected. Losa, et al.[16] reviewed the literature and observed that most cases are in native valves and that the overall mortality rate was not higher than in HIV– patients with IE.

Vegetations vary greatly in size, irrespectively of the etiology, and their size had no relationship to the incidence of heart failure, the risk of death during the acute phase, or the final outcome. Ribera, et al.[15] measured the size of vegetations in a group of HIV+ and HIV– patients with IE, and there were no differences between the two groups. There are no other studies with vegetation-size evaluations and its prognostic implications.

Table 2 shows the different valvular involvement observed in three recent series of IVDA patients with IE, with and without HIV infection.

Clinical characteristics

Endocarditis can cause a wide variety of symptoms, particularly in the earlier stages of infection. Clinical characteristics do not differ significantly by HIV serostatus. The disease begins acutely and patients may experience such general symptoms as fever, chills, fatigue, weight loss, muscle aches and sweating. Fever is the most important and frequent symptom. The mean duration of fever before hospitalization is, in some series, longer in HIV+ patients than in HIV– ones. Mean platelets, leukocyte, neutrophil and CD4+ cells counts are significantly higher in patients with HIV without AIDS and also in subjects without HIV compared to HIV+ individuals, but these findings do not have any prognostic value.

There are some special situations when patients with IE have prolonged fever: 1) sometimes it is possible that an HIV– IVDA subject develops a primary HIV infection while the evolution of IE is favorable, the fever being due to HIV and not IE related; 2) patients with advanced HIV infection can develop many concomitant opportunistic infections like tuberculosis, lymphoma or other febrile diseases that may be misdiagnosed because they will possibly be attributed to IE, and 3) IVDA patients with or without HIV infection may be infected by hepatitis C virus (HCV) and/or hepatitis B

Table 2. Valvular involvement observed in three recent series of infective endocarditic in IVDA patients with and without HIV infection

	Miró, et al. Affected valve in 1529 episodes of IE diagnosed in Spain (1977-1993). Overall HIV+ and HIV–	Ribera, et al. Valvular involvement in 283 episodes of IE in IVDAs		Cicalini, et al. Site of involvement in 108 cases of IE in 105 HIV-infected patients (2001)
		HIV+ (n = 216)	HIV– (n = 67)	
Right sided	1199 (79%)	162 (75%)	30 (44.8%)*	58 (53.7%)
Left sided	254 (16%)	22 (10.2%)	32 (47.8%)*	37 (34.2%)
Mixed side	76 (5%)	16 (7.4%)	5 (7.5%)	12 (11.2%)
Specific location				
– Tricuspid	1045 (68%)	136 (63%)	27 (40.3%)†	56 (51.9%)
– Pulmonic	14 (1%)	5 (2.3%)	—	1 (0.9%)
– Aortic	103 (7%)	12 (5.6%)	19 (28.4%)*	11 (10.2%)
– Mitral	98 (6%)	8 (3.7%)	9 (13.4%)	17 (15.8%)

*$p < 0.001$; †$p < 0.005$.

virus (HBV), producing hepatic enzyme elevations or other clinical manifestations that complicate and make difficult the management of IE[15,17,21,28,35,36].

The clinical manifestations depend mainly on the affected valve and are different between either the right or left location.

Right-sided infective endocarditis

This is the most important in HIV-infected patients, because most subjects are IVDAs and the tricuspid valve is responsible for the clinical manifestations. Heart murmur does not always exist, sometimes making the diagnosis more difficult. Chest pain, cough and pulmonary infiltrates appear with a variable rate (25-70%) and in those series that compare HIV+ and HIV– patients, these findings are always more frequent in the former. Right-heart failure is an uncommon complication. Chest X-rays show septic embolisms in more than 50% of cases, and these embolisms can occur before diagnosis, during therapy, or after therapy is completed. They are usually peripheral and located in inferior lobes (Fig. 1) and there are no differences whether patients are HIV+ or HIV–. These may be cavitated or become associated with pleural effusions or empyema in up to 75% of cases, but pneumothorax is an unusual complication[17-19,22,37,38].

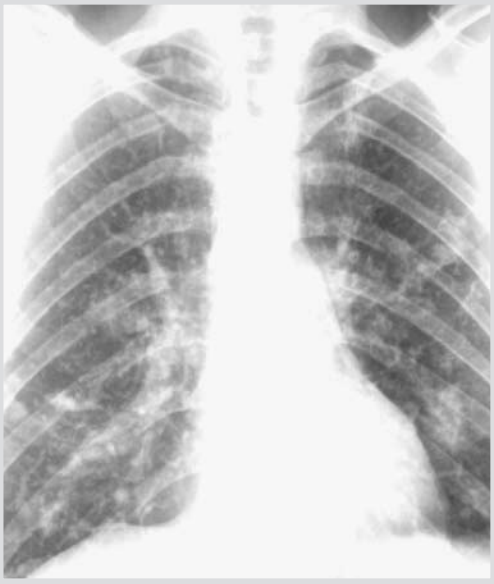

Figure 1. *Chest radiography with several septic pulmonary emboli in a patient with HIV infection, 240 CD4+ cells per mm^3 and right-sided infective endocarditis. Blood cultures were negatives and he was discharged asymptomatic after two weeks of cloxacillin and tobramycin.*

Left-sided infective endocarditis

Left-sided IE in HIV-infected patients has special clinical, epidemiological and microbiological characteristics and its relationship with IVDA subjects is unknown. Murmurs, underlying heart disease, left-heart failure, systemic emboli and peripheral vascular phenomena are frequently present[12,17,18,38]. Valencia, et al.[34] diagnosed 34 cases in a group 190 patients with IE (18%). The presentation was subacute in 70%, the

Table 3. Differences between clinical characteristics and complications of IE in patients with HIV infection depending on the affected valve

	Right-sided endocarditis	Left-sided endocarditis
Clinical manifestations	Symptoms appear acutely: fever, chest pain, cough Heart murmur does not always exists	Symptoms appear sub-acutely: fever, systemic emboli and peripheral vascular phenomena Cardiac murmurs and underlying heart disease are very frequent
Chest X-ray	Septic emboli in more than 50% of cases	Less than 10% have systemic septic emboli
Blood culture	*Staphylococcus aureus* is the most frequent isolated germen in IVDAs	*Staphylococcus aureus* is the most frequent isolated germen in IVDAs
Complications	Right-sided failure is an uncommon complication	Left-sided failure appears in 10-30% of cases
Mortality	Less than 5%	Higher than 15%

patients were severely immunodepressed, and the most important symptom was fever. Only three (9%) had septic emboli in chest X-ray and the affected valve was mitral in 31 patients (91%). This findings are similar to those described by other authors, except Losa, et al.[16], who found aortic involvement as the more frequently affected site in those subjects who were HIV+ and not IVDAs. Sometimes polivalvular involvement (for example mitral and tricuspid) is possible, with symptoms due to both locations and multiple septic emboli in chest X-ray.

Systemic complications

Systemic complications are more frequent in left-sided endocarditis and the need for surgical treatment is more than ten times that observed in right-sided endocarditis[5,12]. The most important complications are congestive heart failure (30%), renal failure (35%), and major systemic emboli that often involve major arterial bed, including coronary arteries, spleen, central nervous system, bowel and extremities. Congestive heart failure (CHF) has the greatest impact on prognosis and occurs more frequently in aortic valve infections (30%) than with mitral (20%) or tricuspid disease (8%). CHF may develop acutely from the perforation of a valve leaflet, rupture of infected chordae or valve obstruction from bulky vegetations. It may also develop more insidiously, despite antibiotics, as a result of a progressive worsening of valvular insufficiency and ventricular dysfunction. This situation is unusual in IVDAs with HIV infection because the affected valve is the tricuspid[5,12,39-41]. For instance, complications are quite different if patients have right-sided or left-sided IE, and if they are HIV+ or HIV–. Ribera, et al.[15] found a statistical significance between HIV+ and HIV– patients in regard to CHF (15.7 vs. 32.8%), renal failure (19.9 vs. 37.3%) and surgical treatment (7.4 vs. 23.9%).

Table 3 shows the differences between clinical characteristics and complications of IE in patients with HIV infection depending on the affected valve.

Diagnosis

The diagnosis of IE is straightforward in those patients with classic manifestations: bacteremia or fungemia, evidence of active valvulitis, septic emboli and immunologic vascular phenomena. In other patients, however, the classic peripheral stigmata may be few or absent. This is typically observed during acute courses of IE, particularly among IVDA patients, with or without HIV infection, in whom IE is mainly due to *S. aureus* and located in right-sided valves.

Infective endocarditis may be definitely diagnosed when a patient has positive blood cultures and new vegetations in echocardiography. Sometimes, at diagnosis it is not possible to find vegetations, and then right-sided IE is suspected when *S. aureus* is isolated in blood cultures in an IVDA subject with septic pulmonary emboli, even though cardiac murmur or peripheral stigmata are not present. Left-sided IE has the same signs and symptoms as in the general population. These situations all included IE in the clinical, microbiological and echocardiographic criteria published by Durack, et al. in 1994[42]. These Dukes criteria combine the important diagnostic parameters contained in the Beth Israel criteria (persistent bacteremia, new regurgitant murmur and vascular complications) with echocardiographic findings. Moreover, i.v. drug use is recognized as an increasingly important, underlying, comorbid condition for development of IE[39,42,43].

Two-dimensional echocardiography and positive blood cultures are the principal tools for diagnosing IE in IVDAs and the features are concordant in more than 80% of cases. The transesophageal technique is more sensitive than transthoracic, but in practice the latter is performed first because it is easier and cheaper and the detection of tricuspid vegetations is similar with both techniques[5,39,40].

It is very important not to confuse right-sided IE with community-acquired pneumonia, tuberculosis or *Pneumocystis carinii* pneumonia, where respiratory symptoms are, in these diseases and in right-sided IE, the most important clinical manifestations[5,15-19].

Prognosis

Mortality depends on the affected valve and the responsible agent, and when it is located on the tricuspid valve and caused by *S. aureus*, the prognosis is good with a mortality rate between 5-10%. The evolution in patients with pulmonic valve infection is similar that observed in those with tricuspid valve involvement. When the left side is affected, the diagnosis is more difficult and mortality increases to more than 15-18%. Although, in general, HIV infection does not affect the clinical manifestations or evolution of IE, the presence of AIDS or CD4+ lymphocytes below 200 per mm^3 predicts a worst prognosis. Cardiac surgery is not usually necessary (complicated left-sided IE, fungal disease, etc.) and does not worsen the prognosis[22,27,40,44-46].

Treatment

Medical management

The treatment is similar to that used with other groups of IE patients, but *S. aureus* must always be considered because it is the most common microorganism on both sides of the heart. The choice of empirical therapy depends on clinical suspicion and generally a penicillinase-resistant penicillin (cloxacillin 2 g i.v./4 h or nafcillin 2 g i.v./4 h) associated with an aminoglycoside antibiotic (gentamicin 80 mg i.v./8 h) is recommended. It is necessary to add ampicillin (2 g i.v./4 h) or ceftriaxone g i.v./day) when left-sided involvement is suspected. Afterwards, the therapy may be changed (if necessary) depending on blood culture data and antibiotic susceptibility[47-51].

Left-sided IE in IVDAs with or without HIV infection is similar to that in the general population. It must be treated for a longer time than right-sided IE, the therapy duration will be at least four weeks and could be prolonged for six weeks if the patient has developed one or several complications[5,39,40,51,52].

The most frequent situation is an IVDA patient with right-sided IE and blood culture with methicillin-susceptible *S. aureus* (MSSA) isolation. In this case it is possible to employ a two-week course of combination therapy with cloxacillin 2 g i.v./4 h plus gentamicin 80 mg i.v./8 h. There are some studies that obtain similar results only with cloxacillin monotherapy, but the use of an aminoglycoside for the first 5-7 days is recommended. This association may have some therapeutic value due to its synergistic effect, with faster microbial eradication and shorter fever duration[40,53-56]. However, there are exclusion criteria for the two-week course of combination therapy for MSSA right-sided IE and Miró, et al.[18] recommend the standard four-week regimen in these situations:

1. Slow response to initial therapy.
2. Complicated right-sided endocarditis.
3. Therapy with antibiotics other than penicillinase-resistant penicillin.
4. Right-sided IE caused by methicillin-resistant *S. aureus (MRSA)* or polymicrobial infections.
5. IVDAs with severe immunosuppression or AIDS.

Sometimes the patient is an allergic subject, or IE is caused by MRSA and it is not possible to use penicillinase-resistant penicillin. In these cases, the treatment must be vancomycin (1 g/12 h) or teicoplanin (400 mg/12 h for 1-3 days and then 400 mg per day) during four weeks plus an aminoglycoside for the first days. It is important to remember that people who are addicted to drugs, and with MSSA right-sided endocarditis treated with vancomycin or teicoplanin, have an unacceptable failure rate. This is the same for left-sided involvement and MRSA infections[18,57,58]. There are several explanations for glycopeptide treatment failure of MSSA endocarditis in IVDAs:

1. Glycopeptides are less rapidly bactericidal against MSSA compared to penicillinase-resistant penicillin.
2. Glycopeptides have a poor diffusion into valve vegetations.
3. The renal clearance of glycopeptides in IVDAs is greater than in non-IVDA volunteers.

For all those reasons, IVDAs with IE treated with these drugs should be monitored closely to check the effectiveness of the treatment. Therefore, vancomycin or teicoplanin should be used only in patients with allergy to penicillin, should be given for at least four

Table 4. Medical management of infective endocarditis in intravenous drug addicts patients with and without HIV infection

Side of the heart involved	Most probable organisms	Initial antibiotic therapy
Right/mixed	Common: *S. aureus* Less common: *P. aeruginosa, streptococci, Candida*, other bacteria	Cloxacillin 2 g i.v./4 h or nafcillin 2 g i.v./4 h + gentamicin 80 mg i.v./8 h
Left	Common: *S. aureus, streptococci, enterococci* Less common: *P. aeruginosa,* other gram negative bacilli, *Candida*, other bacteria	Ampicillin 2 g i.v./4 h or ceftriaxone 2 g i.v./24 h + cloxacillin 2 g i.v./4 h or nafcillin 2 g i.v./4 h + gentamicin 80 mg i.v./8 h
Special situations		
– Methicillin-resistant *S. aureus*		Vancomycin 1 g i.v./12 h + gentamicin 80 mg i.v./8 h
– Oral treatment for methicillin-sensible *S. aureus* and right-sided endocarditis		Ciprofloxacin 750 mg/12 h + rifampicin 600 mg/day

weeks, and gentamicin should be added during the first 1-2 weeks of therapy.

Patients who refuse hospitalization, or who are not severely ill, can be treated successfully with ciprofloxacin (750 mg/12 h) plus rifampin (600 mg per day) given orally for four weeks. This treatment can only be used if the IE is right-sided *S. aureus*, if the patient has a good compliance and is not receiving methadone (presumable interaction with rifampin), and it should be taken into account that resistance to one or both drugs during the treatment has been described[59-61].

Surgical management

A few years ago, a patient with active drug addiction and IE would have been refused for surgery due to the bad prognosis, conditioned by the continuous risk of recurrent IE through the follow-up after intervention and the presence of a concomitant disease with high mortality: HIV infection. Now the situation has changed, and the surgical prognosis of these types of patients is better because there are effective detoxification programs for IVDAs, and the prognosis of HIV infection has dramatically improved with HAART[62,63]. Mestres, et al.[62] published a retrospective analysis of 31 HIV-infected patients undergoing cardiac surgery for different diseases and observed a mortality of 50% in those with active IE. However, they noticed a steady increase in the number of subjects with HIV infection who are referred for surgery.

The indications for surgery and the technical options for left-sided IE are the same as in the general population[64,65]. Furthermore, two special issues are usually taken into account before considering surgery in this population: the likelihood of continuing i.v. drug abuse, with continuing risk of reinfection, overdose and other complications, and the issue of HIV infection. In the case of right-sided IE, there are two surgical indications: 1) endocarditis caused by microorganisms difficult to eradicate, such as fungal etiology or persistent bacteremia, and 2) patients with large tricuspid vegetations, with dilated right ventricle and recurrent pulmonary emboli. The technical options for right-sided IE are conservative and most surgeons opt to avoid the implantation of foreign material because a lot of patients will continue being IVDAs and the risk for a new episode of IE is higher[64-66]. In recent years, tricuspid valve replacement with cryopreserved mitral homografts has emerged as the latest technical option for tricuspid valve replacement. In this case the rationale is to avoid implantation of foreign material and the operation is conceptually and practically simple and provides competence of the right atrioventricular orifice, thus eventually avoiding later right-heart failure due to persistent massive regurgitation[67,68].

Table 4 summarizes the medical management of IE in IVDAs, which is the same with or without HIV infection, and table 5 shows the indications for surgery in patients with HIV and IE.

Influence of HIV infection

The prevalence of HIV-1 infection among IVDAs with IE ranges between 40 and 90%. For instance, although IVDAs are the most important risk group for also acquiring HIV infection, the full consequences are not yet fully known because there are only a few retrospective studies that review the clinical and epidemiological characteristics of IE in these patients.

Table 5. Indications for surgical management in patients with HIV and active IE

1. Left-sided endocarditis
   – Valvular dysfunction with valvular insufficiency and/or congestive heart failure
   – Perivalvular extension with heart block, fistula or abscesses formation
   – Persistent vegetation after systemic embolization or increase in vegetation size after four weeks of antimicrobial therapy

2. Right-sided endocarditis
   – IE caused by microorganism difficult to eradicate (fungi, persistent bacteremia)
   – Patients with large tricuspid vegetations with dilated right ventricle, right-ventricle failure and recurrent pulmonary emboli

Incidence

Several epidemiologic studies have shown that HIV infection is associated with a several-fold increased risk of IE in IVDAs. Manoff, et al.[21] showed that, compared with HIV– IVDAs, HIV+ IVDAs with CD4+ cell counts of 350 per mm^3 or more had less risk for developing IE than those with a CD4+ cell count below 350 per mm^3. These findings have been confirmed by Wilson, et al.[12], who found that IE is more common among IVDAs with advanced HIV immunosuppression, even after taking into account injection drug use behaviors.

Clinical characteristics and etiology

The presence of HIV infection does not alter the clinical manifestations and the febrile response of IVDA patients with IE. This finding was observed, for example, by Nahass, et al.[69] and Valencia, et al.[17], who concluded that IE is usually reported in the early stages of HIV infection and apparently its presence has no influence on the clinical course of IE. However, HIV+ patients have lower white blood cell counts, mainly lymphocytes and platelets, and a higher ratio of right-sided IE and *S. aureus* infections than HIV– IVDAs[15,17, 68].

Medical management

Response to antimicrobial therapy is similar in patients with and without HIV infection. It is not known, however, if right-sided MSSA endocarditis can be treated successfully with short-course therapy in HIV+ IVDAs. Ribera, et al.[53] and Fortún, et al.[54] showed that cure rates for asymptomatic HIV+ IVDAs were the same as for HIV– IVDAs in a group of patients with a median CD4+ cell count of nearly 300/mm^3. Although these data are very promising, the reality is that there is not enough information about the efficacy of this short-course regimen in patients with AIDS or severely immunodepressed subjects (CD4+ cells < 200 mm^3).

Surgical management

The presence of HIV infection does not seem to worsen the surgical prognosis in HIV-infected IVDA patients with IE. When cardiac surgery is necessary for treating a complicated right-sided IE, the most recommended techniques are tricuspid valvulectomy without prosthetic replacement and tricuspid valve replacement with cryopreserved mitral homografts. Left-sided IE has the same indications and surgical techniques as in the general population.

Prognosis

Nahass, et al.[69] found that the mortality was higher in patients with symptomatic HIV disease, and Valencia, et al.[17] found a similar rate of mortality in patients with and without HIV infection. Pulvirenti, et al.[70] reported that IE in IVDAs with HIV infection had a differing outcome depending on the degree of immunosuppression, and that higher mortality rates correlated with lower CD4+ cell counts. Ribera, et al.[15], in a prospective study in 1998, observed that outcome was similar according to HIV serostatus, but mortality was higher in the severely immunosuppressed patients and in those with mixed or left-sided involvement. Cicalini, et al.[28] reviewed 108 episodes of IE in 105 patients with HIV infection and also observed that severe immunosuppression and left-sided valvular involvement are associated with a greater risk of mortality.

Acknowledgments

Dr. José M.ª Miró was a recipient of a Research Grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona (Spain).

References

1. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced HIV infection. HIV outpatient Study Investigators. N Engl J Med 1998;338:853-60.
2. Ives N, Gazzard B, Easterbrook P. The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. J Infect 2001;42:134-9.
3. Iribarren J, González J. Ingresos hospitalarios y mortalidad en pacientes con sida en la era TARGA: ¿hacia dónde vamos? Enferm Infecc Microbiol Clin 2004;22:129-32.
4. Haverkos H, Lange W. Serious infections other than HIV among intravenous drug users. J Infect Dis 1990;161:894-902.
5. Tanner D, Durack D. Infective endocarditis. Curr Opin Infect Dis 1990;3:643-52.
6. Cherubin C, Saira J. The medical complications of drug addiction and the medical assessment of the intravenous user: 25 years later. Ann Intern Med 1993;119:1017-28.
7. Mesa R, Edell E, Dunn W, Edwards W. HIV infection and pulmonary hypertension: two new cases and a review of 86 reported cases. Mayo Clin Proc 1998;73:37-45.
8. Valencia M, Ortega G, Guinea J, et al. Hipertensión pulmonar en los pacientes con infección por el virus de la inmunodeficiencia humana. Estudio de 14 casos. Med Clin 2000;115:181-4.
9. Rerkpattanapipat P, Wongpaparut N, Jacobs L, Kotler M. Cardiac manifestations of acquired immunodeficiency syndrome. Arch Intern Med 2000;160:602-8.
10. Flotats A, Domingo P, Carrió I. Afección cardíaca en la infección por el virus de la inmunodeficiencia humana. Med Clin (Barc) 1999;113:383-90.
11. Wilson L, Moore R, Burkey M, Gebo K. The incidence of and risk factors for infective endocarditis (IE) in an urban HIV cohort. 11th CROI. San Francisco, CA, February 8-11, 2004 [abstract 877].
12. Wilson L, Thomas D, Astemborsky J, Freedman T, Vlahov D. Prospective study of infective endocarditis among injection drug users. J Infect Dis 2002;185:1761-6.
13. Valencia M, Guinea J, Moreno V, González-Lahoz J. Absceso miocárdico sin lesión valvular concomitante y adicción a drogas por vía parenteral. Rev Clin Esp 1992;191:289.
14. Valencia M. Endocarditis infecciosa en drogadictos. Rev Clin Esp 1995;195:128-9.
15. Ribera E, Miró J, Cortés, et al. Influence of HIV-1 infection and degree of immunosuppression in the clinical characteristics and outcomes of infective endocarditis in intravenous drug users. Arch Intern Med 1998;158:2043-50.
16. Losa J, Miró J, Del Río A, et al. Infective endocarditis not related to intravenous drug abuse in HIV-infected patients: report of eight cases and review of the literature. Clin Microbiol Infect 2003;9:45-54.
17. Valencia M, Guinea J, Soriano V, et al. Estudio de 164 episodios de endocarditis infecciosa en drogadictos: comparación entre pacientes VIH positivos y negativos. Rev Clin Esp 1994;194:535-9.
18. Miró J, Del Río A, Mestres C. Infective endocarditis in intravenous drug abusers and HIV-1 infected patients. Infect Dis Clin North Am 2002;16:273-95.
19. Currie P, Sutherland G, Jacob A, Bell J, Brettle R, Boon N. A review of endocarditis in acquired immunodeficiency syndrome and HIV infection. Eur Heart J 1995;16(Suppl B):15-8.
20. Torres-Tortosa M, Rivero A, De Alarcón A, Vergara A, Lozano F, Reguera J. Decrease in the annual frequency of infectious endocarditis among intravenous drug users in southern Spain. Enferm Infecc Microbiol Clin 2000;18:293-4.
21. Manoff S, Vlahov D, Herskowitz A, et al. HIV infection and infective endocarditis among injecting drug users. Epidemiol 1996;7:566-70.
22. Mathew J, Addai T, Anand A, Morrobel A, Maheshwari P, Freels S. Clinical features, site of involvement, bacteriologic findings and outcome of infective endocarditis in intravenous drug users. Arch Intern Med 1995;155:1641-8.
23. Miró J, Cruceta A, Gatell J. Infective endocarditis (IE) in Spanish i.v. drug addicts (IVDA): analysis of 1.529 episodes (1978-1993). Third International Symposium on Modern Concepts in Endocarditis. Boston, Massachusetts, July 13-15, 1995:32 [abstract 109].
24. Valencia M, Guinea J, Enríquez A, González-Lahoz J. Endocarditis por *Streptococcus pneumoniae. Med Clin (Barc) 1994;102:277-8.*
25. Soriano V, Valencia M, Alba A, González-Lahoz J. Endocarditis por Xanthomonas maltophilia. Med Clin (Barc) 1994;102:399.
26. Bisbe J, Miró J, Latorre X, et al. Disseminated candidiasis in addicts who use brown heroin: report of 83 cases and review. Clin Infect Dis 1992;15:910-23.
27. Bouza E, Menasalvas A, Muñoz P, Vasallo F, Del Mar M, García M. Infective endocarditis: a prospective study at the end of the twentieth century – new predisposing conditions, new etiologic agents and still a high mortality. Medicine (Baltimore) 2001;80:298-307.
28. Cicalini S, Forcina G, Rosa F. Infective endocarditis in patients with HIV infection. J Infect 2001;42:267-71.
29. Valencia M, Enríquez A, Guinea J, González-Lahoz J. Endocarditis polimicrobiana: estudio clínico y evolutivo de doce casos diagnosticados durante un período de 10 años. Rev Clin Esp 1997;197:245-7.
30. Daniel W, Mügge A, Martin R, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795-803.
31. Mügge A, Daniel W, Frank C, Lichtlen P. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetations size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol 1989;14:631-8.
32. Valencia M, Guinea J, Soriano V, González-Lahoz J. Endocarditis sobre válvula pulmonar en drogadictos. Rev Clin Esp 1995;195:884-5.
33. Moreillon P, Que Y, Bayer A. Pathogenesis of streptococcal and staphylococcal endocarditis. Infect Dis Clin North Am 2002;16:297-318.
34. Valencia M, Guinea J, Enríquez A, Moreno V, Laguna F, González-Lahoz J. Endocarditis de válvulas izquierdas en pacientes con infección por VIH. Ann Intern Med (Madrid) 1999;4:171-4.
35. Watanakunakorn C, Burket T. Infective endocarditis at a large community teaching hospital, 1980-1990: a review of 210 episodes. Medicine (Baltimore) 1993;72:90-102.
36. Miró J, Engemann J, Cabel C, et al. Intravenous drug use and infective endocarditis: report from the ICE investigators. Sixth International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections. Sitges (Barcelona, Spain), June 2001.
37. De Alarcón A, Villanueva J. Endocarditis en adictos a drogas por vía parenteral. Endocarditis derecha. Influencia de la situación VIH. Rev Esp Cardiol 1998;51(Suppl 2):71-8.
38. Torres-Tortosa M, González M, Pérez, et al. Endocarditis infecciosa en heroinómanos en la provincia de Cádiz. Un estudio multicéntrico sobre 150 episodios. Med Clin (Barc) 1992;98:521-6.
39. Bayer A, Bolger A, Taubert K, et al. Diagnosis and management of infective endocarditis and its complications. Circulation 1998;98:2936-48.
40. Moreillon P, Yok-Ai Que. Infective endocarditis. Lancet 2004;139-49.
41. Cabell C, Jollis J, Peterson G, et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002;162:90-4.
42. Durack D, Lukes A, Bright D, and the Duke Endocarditis Service. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994;96:200-9.
43. Bayer A, Ward J, Ginzton L, Shapiro S. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. Am J Med 1994;96:211-9.
44. Miró J, Del Río A, Mestres C. Infective endocarditis and cardiac surgery in intravenous drug abusers and HIV-1 infected patients. Cardiol Clin 2003;21:167-84.
45. Mylonakis E, Calderwood S. Infective endocarditis in adults. N Engl J Med 2001;345:1318-30.
46. Hecht S, Berger M. Right-sided endocarditis in intravenous drug users. Prognostic feature in 102 episodes. Ann Intern Med 1992;117:560-6.
47. Working Party of the British Society for Antimicrobial Chemotherapy. Antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis. Heart 1998;79:207-10.

48. Sande M, Courtney K. Nafcillin-gentamicin synergism in experimental staphylococcal endocarditis. J Lab Clin Med 1976;88:118-24.
49. Rubinstein E, Carbon C, and the Endocarditis Working Group of the International Society of Chemotherapy. Staphylococcal endocarditis – Recommendations for therapy. Clin Microbiol Infect 1998;4:3S27-33.
50. Shanson D. New guidelines for the antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis. J Antimicrob Chemother 1998;42:292-6.
51. Wilson W, Karchmer A, Dajani A, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci and HACEK microorganisms. JAMA 1995;274:1076-713.
52. Wilson W, and the Endocarditis Working Group of the International Society of Chemotherapy. Antibiotic treatment of infective endocarditis due to *viridans* streptococci, enterococci and other streptococci. Clin Microbiol Infect 1998;4:3S56-61.
53. Ribera E, Gómez-Jiménez J, Cortés E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. Ann Intern Med 1996;125:969-74.
54. Fortún J, Navas E, Martínez-Beltrán J, et al. Short-course therapy for right-sided endocarditis due to *Staphylococcus aureus* in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. Clin Infect Dis 2001;33:120-5.
55. Espinosa F, Valdés M, Martín-Luengo M, et al. Right-sided endocarditis caused by *Staphylococcus aureus* in parenteral drug addicts: evaluation of a combined therapeutic scheme for 2 weeks versus conventional treatment. Enf Infect Microbiol Clin 1993;11:235-40.
56. Chambers H, Miller T, Newman M. Right-sided *Staphylococcus aureus* endocarditis in intravenous drug abusers: two-week combination therapy. Ann Intern Med 1988;109:619-24.
57. Franciolli M, Bille J, Glauser M, Moreillon P. Beta-lactam resistance mechanisms of methicillin-resistant *Staphylococcus aureus*. J Infect Dis 1991;163:514-23.
58. Small P, Chambers H. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug abusers. Antimicrob Agents Chemother 1990;34:1227-31.
59. Heldman A, Hartert T, Ray S, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med 1996;101:68-76.
60. Dworkin R, Sande M, Lee B, Chambers H. Treatment of right-sided *S. aureus* endocarditis in intravenous drug abusers with ciprofloxacin and rifampicin. Lancet 1989;2:1071-3.
61. Tebas P, Ruiz M, Román F, et al. Early resistance to rifampin and ciprofloxacin in the treatment of right-sided *Staphylococcus aureus* endocarditis. Ann Intern Med 1991;115:674-80.
62. Mestres C, Chuquiure JE, Claramonte X, et al. Long-term results after cardiac surgery in patients infected with the HIV type-1 (HIV-1). Eur J Cardio-Thor Surg 2003;23:1007-16.
63. Valencia M, Guinea J, Enríquez A, Ortega G, Moreno V, González-Lahoz J. Study of 42 cases of infective endocarditis in the HAART era in Spain. Clin Microbiol Infect 2003;10:1073-5.
64. Alsip S, Blackstone E, Kirklin J, Cobbs C. Indications for cardiac surgery in patients with active infective endocarditis. Am J Med 1985;78(Suppl 6B):138-48.
65. Petterson G, Carbon C, and the Endocarditis Working Group of the International Society of Chemotherapy. Recommendations for the surgical treatment of endocarditis. Clin Microbiol Infect 1998;4:3S34-46.
66. Carrel T, Schaffner A, Vogt P, et al. Endocarditis in intravenous drug addicts and HIV-infected patients: possibilities and limitations of surgical treatment. J Heart Valve Dis 1993;2:140-7.
67. Mestres C, Miró J, Paré J, Pomar J. Six-year experience with cryopreserved mitral homografts in the treatment of tricuspid valve endocarditis in HIV-infected drug addicts. J Heart Val Dis 1999;8:575-7.
68. Miró J, Moreno A, Mestres C. Infective endocarditis in intravenous drug abusers. Curr Infect Dis Reports 2003;5:307-16.
69. Nahass R, Weinstein M, Bartels J, Gocke D. Infective endocarditis in intravenous users: a comparison of HIV type 1 negative and positive patients. J Infect Dis 1990;162:967-70.
70. Pulvirenti J, Kerns E, Benson C, Lisowski J, Demarais P, Weinstein R. Infective endocarditis in injection drug users: importance of human immunodeficiency serostatus and degree of immunosuppression. Clin Infect Dis 1996;22:40-5.