Infective Endocarditis in Intravenous Drug Abusers: Patterns of Presentation and Long-Term Outcomes of Surgical Treatment

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Background and aim of the study: **Few data exist on infective endocarditis (IE) in intravenous drug abuse (IVDA) patients. In particular, clinical features, site of involvement and bacteriologic findings are controversial. Little is also known on the results of surgical treatment and on the long-term prognosis.**
Methods: **The clinical and microbiological characteristics of IE in a series of 39 IVDA patients were retrospectively assessed and compared to those in 85 non-IVDA patients with a likely similar life expectancy. The total follow up of patients was 717.6 patient-years (119.9 pt-yr for IVDA, 597.7 pt-yr for non-IVDA).**
Results: **Although tricuspid involvement was significantly more frequent in IVDA cases than in non-IVDA cases (p = 0.001), left-sided endocarditis prevailed in both groups. In addition to *Staphylococcus aureus* (51.3%), *Staph. epidermidis* (15.4%) and streptococcal spp. (23.1%) were emerging pathogens in IVDA cases. A worse cardiac function (p <0.002) and a higher rate of embolism (p = 0.04) characterized the preoperative status of IVDA patients. No difference was observed as to indications, emergency procedures and pathologic findings. Hospital and long-term survival did not significantly differ between the two groups. The rate of recurrence was higher in IVDA cases; this difference was mostly accounted for by early postoperative events.**
Conclusion: **A new pattern of IE in IVDA is emerging, characterized by more frequent left heart involvement (61.5%), a severe clinical course, and a need for surgery in the active phase. *Staph. epidermidis* and streptococci are emerging pathogens. Drug abuse does not affect postoperative prognosis when an aggressive surgical attitude is combined with prolonged medical therapy. Higher rates of early recurrence are expected during the follow up period.**

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Before the spread of HIV and the resurgence of cocaine use, infective endocarditis (IE) was the second major acute complication of parenteral drug abuse, exceeded only by overdose. The incidence of IE in intravenous drug abuse (IVDA) cases is 2 to 5% per year, with IVDA being responsible for 5 to 20% of hospital admissions and 5 to 10% of the overall mortality rate (1,2). Few data currently exist on IE in this patient subset. In particular, the clinical features, site of involvement and bacteriologic findings are controversial. Although IE is generally assumed to affect mainly the tricuspid valve and to be caused by *Staphylococcus aureus*, recent reports have suggested that the involvement of left-sided valves may be more common than believed, and that other pathogens might contribute substantially to the development of the condition (3). In addition, little is still known with regard to the results of surgical treatment and the long-term prognosis of those patients who survive surgery (4). The study aim was to determine the clinical and microbiological features, as well as the outcome, of IE in IVDA and non-IVDA patients.

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Clinical material and methods

Patients and definitions

All IVDA patients referred for surgical treatment for native valve IE (n = 39) between January 1980 and December 2004 were selected from an electronic database of cardiac procedures at the Department of Cardio-Thoracic and Respiratory Sciences, Second

University of Naples. The study aim was to characterize the pathogenesis, clinical picture and outcome of IE in IVDA cases, and to differentiate them from those of a group of contemporary non-IVDA patients (n = 85) treated for native valve IE. When addressing the issue of prognosis, in order to reduce the confounding impact of some variables on life expectancy, non-IVDA patients with comparable age and activity phase of IE were selected. The diagnosis and definition of IE was based on the major criterion of endocardial involvement in patients with systemic active infection in 92% of cases; in the remaining patients, diagnosis was performed according to other Durack's and modified Aranki's criteria (5-7). Endocarditis was labeled 'active' if the patient had fever, leukocytosis and/or positive blood/valve cultures at the time of surgery, or required surgical treatment before completion of a standard course of antibiotic treatment. Early mortality or morbidity was defined as death or complications occurring within 30 days or during the same hospital stay after surgery. Late mortality and morbidity were classified according to the criteria of Edmund et al. (8).

Surgical technique

The surgical procedures used have been described previously (5,9). In summary, cardiopulmonary bypass, systemic hypothermia and moderate hemodilution were used in all cases. Antegrade crystalloid cardioplegia, along with topical and systemic hypothermia, were the main strategies for myocardial protection. Complete debridement of all infected necrotic tissues, along with a thorough search for subvalvular abscesses and fistula, was always conducted. Mechanical and bioprosthetic valves were implanted with interrupted stitches. The use of pledgeted sutures was limited to cases with periannular involvement.

Postoperative management and follow up

The explanted valves were inspected, and the macroscopic findings recorded for comparison with the preoperative echocardiography report. All infected tissues retrieved at surgery were sent for culture and pathology examination, in order to achieve a definitive diagnosis. All patients underwent intravenous antibiotic therapy for at least four weeks postoperatively. Culture-negative endocarditis was usually treated with combinations of broad-spectrum antibiotics. Patients with positive cultures were treated according to susceptibility tests. Early postoperative management and clinico-instrumental follow up were performed in coordination with a dedicated bacterial infection unit. Patients were followed up through an accurate periodical check of possible origins of infectious processes and short-interval echocardiography controls to exclude recurrent vegetations or paravalvular leaks.

Data acquisition

Data regarding hospitalization were obtained from hospital record charts. Data related to outcome after discharge and clinical status at follow up were obtained from outpatient clinic records or by telephone interviews, either to the patients or to the general practitioner/referring physician, or both. Preoperative variables recorded included: age, gender, serological positivity to HIV, hepatitis B virus (HBV) and/or hepatitis C virus (HCV), drug addiction, renal function impairment, blood culture results, previous major embolism, site of endocarditis, hemodynamic/clinical conditions, and 'active'/'healed' endocarditis. The operative variables recorded included: condition indicating surgery, urgency/emergency operation, surgical findings, and operative technique (prosthetic replacement/valve repair, type of valve substitute implanted). Postoperative and follow up variables recorded included: early mortality, major complications, tissue culture results, mortality at follow up, recurrence of endocarditis, and reoperation.

Statistical analysis

Statistical analyses were performed using SPSS software (version 10.1; Chicago, IL, USA). Data were expressed as mean (± SD), or counts and percentages when appropriate. Differences in categorical variables were assessed by means of the χ^2 or Fisher's exact test. Continuous variables were analyzed with a two-tailed Student's *t*-test. The likelihood ratio test was used to compare time-linearized (% per patient-year) postoperative events. Cumulative survival and complications were computed by means of actuarial curves using the product limit method, and estimated hazard functions were presented. Statistical significance was defined as a p-value ≤0.05.

Results

Patient characteristics, microbiological and surgical pathology findings

The demographics and preoperative features of the IVDA and non-IVDA groups are summarized in Table I. The IVDA patients were mostly males, and showed a significantly higher prevalence of liver comorbidity (notably hepatitis C). Among the drugs used by IVDA patients, heroin was reported in 100% of cases and cocaine in 41%. The preoperative picture of drug abusers was usually worse: cardiac decompensation was more pronounced (30.8% were NYHA class IV or V compared to 11.8%; p <0.002), and there was an higher incidence of preoperative embolic events (53.8% versus 35.3%; p = 0.04) with preferential involvement of the pulmonary arterial system. With regard to location of the disease, among IVDA patients

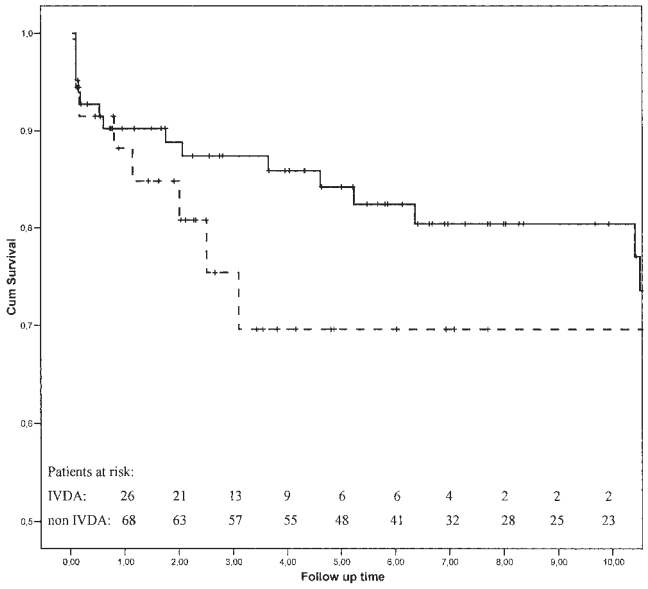

Figure 1: Cumulative actuarial survival of the study groups (broken line, IVDA cases; solid line, non-IVDA cases).

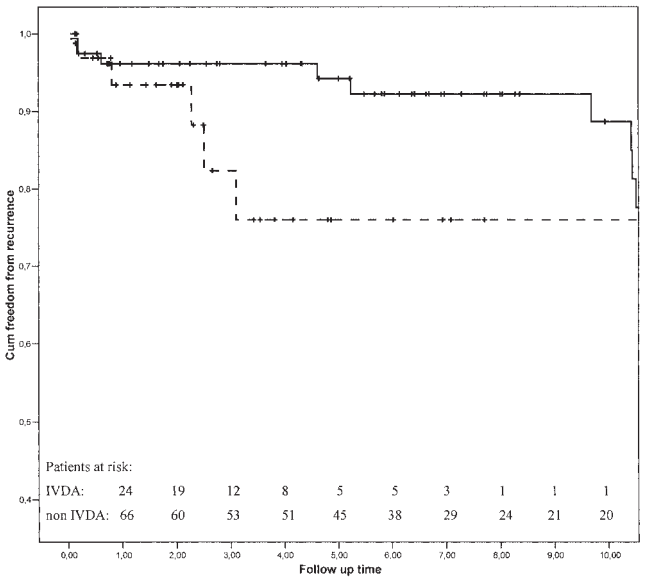

Figure 2: Freedom from recurrence of infective endocarditis (broken line, IVDA cases; solid line, non-IVDA cases).

Table I: Patient demographic and preoperative data.

Parameter	IVDA (n = 39)	non-IVDA (n = 85)	p-value
Female gender	4	28	0.005
Age (years)*	32.1 ± 8.1	33.4 ± 8.2	0.270
HCV positivity	26 (66.7)	1 (1.2)	<0.001
HBsAg positivity	3 (7.7)	5 (5.9)	0.487
Previous embolic events	21 (53.8)	30 (35.3)	0.04
Cerebral	3 (14.3)	15 (50)	
Pulmonary	8 (38.1)	3 (10)	
Splenic	5 (23.8)	8 (26.7)	
Others	5 (23.8)	4 (13.3)	
NYHA class			0.002
I	-	-	
II	9 (23.1)	38 (44.7)	
III	18 (46.2)	37 (43.5)	
IV	11 (28.2)	5 (5.9)	
V	1 (2.6)	5 (5.9)	
Septic shock	9 (23.1)	16 (18.8)	0.373
Acute renal failure	3 (7.3)	6 (7.1)	0.581
Site of endocarditis			
Aortic	17 (43.5)	42 (49.4)	0.508
Mitral	4 (10.3)	25 (29.4)	0.005
Tricuspid	11 (28.2)	4 (4.7)	0.001
Multivalvular	7 (18)	14 (16.5)	0.45
Mitro-aortic	3	11	
Mitro-tricuspid	1	1	
Aorto-tricuspid	3	2	
Active endocarditis	39 (100)	85 (100)	

*Values are mean ± SD.
Values in parentheses are percentages.
HBsAg: Hepatitis B surface autigen; HCV: Hepatitis C virus.

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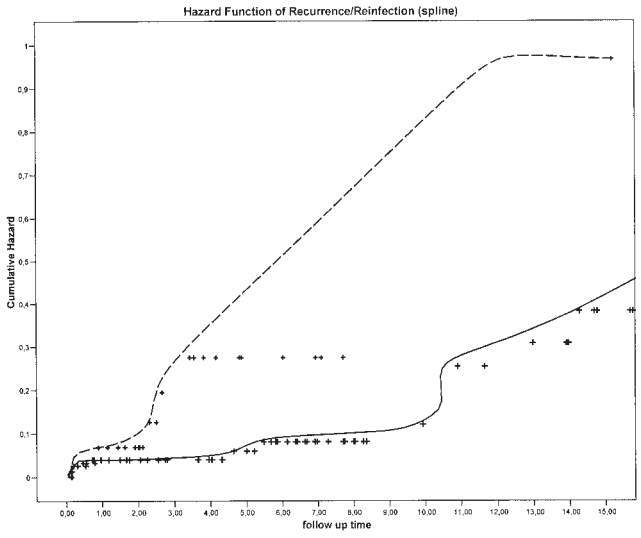

Figure 3: Cumulative hazard function for recurrence of infective endocarditis (broken line, IVDA cases; solid line, non-IVDA cases).

left-side involvement was seen in up to 61.5% of cases. There was no inter-group difference in terms of aortic involvement, while mitral infection was more common in non-IVDA patients (10.3% versus 29.4%; p = 0.005). Tricuspid endocarditis occurred more frequently in the IVDA group (28.2% versus 4.7%; p = 0.001).

Operative characteristics are listed in Table II. The time from symptom onset to surgical treatment was significantly longer in IVDA patients (p = 0.004). No difference emerged as to the indication for surgery and the rate of emergency operations. Surgical pathology disclosed no difference as to the presence of vegetations and abscesses. Although mechanical prostheses represented the most commonly employed replacement device in both groups, bioprosthetic replacement was favored in IVDA cases (41% versus 11.8%; p = 0.001).

The causative agents, as shown by blood cultures, are detailed in Table III. Blood cultures were negative in 7.7% of IVDA cases and in 21.2% of non-IVDA cases (p = 0.05). Among IVDA patients, staphylococci were isolated in 26 cases (66.7%) and streptococci in nine cases (23.1%). Thirteen out of 20 *Staph. aureus* strains isolated were methicillin-resistant (MRSA).

Hospital and long-term outcomes

Overall hospital mortality among IVDA patients was 5.1% (two patients died from multiorgan failure). Similar outcomes were detected in non-IVDA patients (three deaths, 3.5%: one patient died from sepsis and two patients from heart failure). Five patients were lost to follow up, without significant inter-group differences (three IVDA patients (8.1%) versus two non-IVDA (2.4%)); thus, follow up was 95.8% complete. The mean follow up was 6.03 ± 5.7 years (3.14 ± 3.3 years for IVDA; 7.28 ± 6.1 years for non-IVDA; p <0.0001); total follow up was 717.6 patient-years (pt-yr) (119.9 pt-yr for IVDA, 597.7 pt-yr for non-IVDA).

The long-term outcomes were more favorable in the non-IVDA group. Actuarial survival at one, three, five and 10 years was 88.2 ± 0.06%, 75.4 ± 0.08%, 69.6 ± 0.09% and 69.6 ± 0.09% respectively in IVDA patients, and 90.2 ± 0.03%, 88.8 ± 0.03%, 84.2 ± 0.04% and 80.4 ±

Table II: Operative characteristics.

Parameter	IVDA (n = 39)	non-IVDA (n = 85)	p-value
Symptom-surgery interval (months)*	8.53 ± 5.1	5.21 ± 3.7	0.004
Indication for surgery			0.13
Moderate/severe hemodynamic impairment	22 (56.3)	38 (44.7)	
Uncontrolled infection	4 (10.3)	12 (14.1)	
Recurrent major embolism	9 (23.1)	16 (18.8)	
Echocardiographic findings	4 (10.3)	19 (22.4)	
Emergency operation	7 (17.9)	9 (10.6)	0.197
Valve substitute			
Mechanical	22 (56.4)	68 (80)	0.007
Biological	16 (41)	10 (11.8)	0.001
Homograft	-	2 (2.4)	0.468
Valve repair	1 (2.6)	5 (5.9)	0.470
Abscess presence	8 (20.5)	10 (11.8)	0.156
Vegetation	36 (92.3)	77 (91.7)	0.605

*Values are mean ± SD.
Values in parentheses are percentages.

Table III: Preoperative blood culture results.

Organism	IVDA (n = 39)	non-IVDA (n = 85)	p-value
Staphylococcus spp.	26 (66.7)	23 (27)	<0.001
Staph. aureus	20	11	
Coagulase-negative	6	12	
Streptococcus spp.	9 (23.1)	30 (35.3)	0.12
Strep. viridans	1	10	
Strep. bovis	-	2	
Strep. pneumoniae	1	1	
Others	7	17	
Enterococcus faecalis	1	6	
Gram-negative	-	4 (4.7)	
Brucella-	1		
Pseudomonas-	1		
Proteus		-	2
Others	-	4 (4.7)	
Negative	3 (7.7)	18 (21.2)	0.05

Values in parentheses are percentages.

0.05% respectively in non-IVDA patients (Fig. 1). The time-linearized mortality was 8% per pt-yr in IVDA cases, and 3.5% per pt-yr in non-IVDA cases (p = 0.14). Causes of late death among IVDA cases were cardiac decompensation (n = 1), stroke (n = 1), IE recurrence (n = 4) and overdose (n = 1). Causes of late death among non-IVDA cases were cardiac decompensation (n = 9), stroke (n = 1), IE recurrence (n = 4), lung cancer (n = 3) and homicide (n = 1).

Freedom from endocarditis recurrence/reinfection at one, three, five and 10 years was 93.4 ± 0.04%, 82.3 ± 0.08%, 76.0 ± 0.09% and 76.0 ± 0.09% respectively among IVDA patients, and 96.1 ± 0.02%, 96.1 ± 0.02%, 94.2 ± 0.03% and 88.7 ± 0.05% respectively among non-IVDA patients (Fig. 2). The time-linearized events were 6% per pt-yr in IVDA cases, and 2% per pt-yr in non-IVDA cases (p = 0.038). Cumulative hazard function for IE recurrence among the study populations is illustrated in Figure 3. Abstinence from drug and social rehabilitation was achieved by five long-term survivors.

Discussion

Despite IE being the second major acute complication of parenteral drug abuse, few data are available on the clinical and microbiological findings of the condition, or on the role of surgical treatment. Moreover, the available data relating to long-term outlook are both limited and controversial. The most important findings of the present study were that: (i) besides the well-known tricuspid involvement, the incidence of pure left-sided valve infection may reach 61.5%; (ii) microorganisms other than *Staph. aureus* contribute substantially to the pathogenesis of IE; (iii) drug abuse appears not to jeopardize the chances of survival after surgery, both in-hospital and over the long-term follow up; and (iv) the rate of recurrence is significantly higher than that reported in non-IVDA cases, with early postoperative events mostly accounting for this difference.

With regard to valve involvement, right-sided valvular infections have been long considered the hallmark of IE in IVDA patients (10). However, left-sided valve involvement has been increasingly described (3,4), and the rate of pure mitral and/or aortic involvement in the present series was in keeping with the results of necropsy studies (11,12) and other clinical series (13). In particular, aortic valve involvement was similar between the two groups, while there were more mitral and fewer tricuspid infections in non-IVDA cases. The reason for this changing pattern is far from being elucidated; in the authors' clinical practice drug abuse is associated with a generally poor quality of life and poor personal health care. In addition to the direct pathogenetic mechanism of injecting particulate matter and bacteria, drug abuse may also indirectly predispose patients to IE by being associated with other risk factors (e.g. dental, urinary, skin infections). Notably, no significant differences were found in the prevalence of streptococcal species between the two study groups.

Recent reports of bacteriologic findings have been controversial, with differences in causative pathogens being mainly related to different regional and temporal referral conditions and local injection practices (14). An overview of recently published literature disclosed that injectors develop infections due to pathogens sim-

ilar to non-injectors (15). It has been suggested that *Staph. aureus* which, in most series, accounts for 50-70% of IE cases, probably originates from the patient's own skin. A high proportion of IVDA patients are skin carriers of MRSA, as are other types of patient who receive frequent injections. In contrast, some evidence exists that other bacteria and fungi may be derived from the injected material or the diluent (14).

Increasingly, fungal pathogens are seen with immunodeficiency (16). It should be noted that the present series included a high proportion of culture-negative cases: it is possible that this figure hid the expected prevalence of fungal etiology which, in a review of the world literature (17), has been associated with mistaken or delayed diagnosis in up to 82% of cases. In the present study the significant differences in pathogens between IVDA and non-IVDA cases may all relate to specific group features (injection habits in the former population; invasive dental, gastrointestinal and urological maneuvers in the latter population). In contrast with previous reports, no difference emerged as to any specific valve involvement of each etiologic agent between the two study groups (18).

Few data are available on the results of surgical treatment for IE in IVDA patients, and little is known on the long-term outlook in these cases (4,19,20). Preoperative clinical conditions are well-known determinants of perioperative mortality (4,9,21). Despite the high risk admission profile, in-hospital mortality was 5.1%, and close to that observed in non-IVDA cases. Similar outcomes have been reported (4) and are indicative of improvements in combined medical and surgical strategies, as well as of postoperative care and of the relevant specific caseload of the center (5,9,22). Some aspects of surgical treatment may deserve further comment. The implantation of a mechanical prosthesis, which by policy represented the more common strategy in both study groups, proved to be a safe procedure when performed with concomitant radical debridement and aggressive antibiotic therapy. These results are in accordance with those forwarded by the UK Heart Valve Registry (23) and the authors' previous experience (22). Nevertheless, IVDA patients underwent significantly more bioprosthesis implantations, mainly due to the poor compliance of IVDA patients to whatever medical schedule. Given the satisfactory mid-term survival registered in this follow up, the shortcomings of such device selection in a young population are to be expected.

The described rates of recurrence are encouraging and comparable to most published data in the general population (9,24). However, actuarial freedom from recurrence/reinfection was lower in IVDA patients, with a clear trend towards an earlier onset of the disease, as noted previously (24). It should be noted that five out of six recurring events were seen in staphylococcal endocarditis due to MRSA, a well-known predictor of treatment failure, and none of these was linked to the resumption of drug usage.

Study limitations

Some limitations of this study must be considered. First, its retrospective design may have affected outcome analysis. An overview of such a long-term experience must at least take into account the effects of the equipment learning curve and the development of new strategies for diagnosis and treatment. However, as reported previously (5,9,24), the study failed to show any impact of treatment on main outcome (i.e., recurrence). A second limitation was the lack of any report on injection practices which may, to some degree, have influenced microbiological findings (14). Moreover, the mean follow up in the IVDA group was significantly shorter, and very few patients reached 10 years of follow up; hence, the comparison of long-term results might be less reliable than mid-term comparisons. Finally, the higher rate of negative cultures compared to other series must be acknowledged: the authors' center is a tertiary care facility, to which patients were frequently referred from small peripheral institutions, to undergo surgical treatment, often on an emergency basis. Poor standard methods of blood sampling and culturing, especially during the early period of the study, along with untimely broad-spectrum antibiotic therapy performed at the referral centers, might account for culture-negative cases in this series.

In conclusion, the pattern of IE in IVDA which emerged from the present study was characterized by more frequent left heart involvement than previously reported, a severe clinical course, and a need for surgery in the active phase. *Staph. epidermidis* and streptococci proved to be emerging pathogens. Drug abuse did not affect the postoperative prognosis when an aggressive surgical attitude was combined with prolonged medical therapy. Further studies to determine the optimal timing for surgery and best replacement device are warranted.

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