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Title page

Long-term outcomes are poor in intravenous drug users following infective endocarditis, even after surgery.

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Summary: Whilst early survival for people who inject drugs with infective endocarditis is good, long-term survival is poor due to ongoing infection risk. Surgery conferred no long-term survival advantage, so more efforts are needed to reduce re-infection risks for PWID.

Abstract

Words: 252

Background

Previous studies of outcomes in people who inject drugs (PWID) with infective endocarditis (IE) have often been retrospective, had a small sample size, the duration of follow-up has been short and limited to patients who were operated on.

Methods

PWID treated for IE between 01/01/2006 and 31/12/2016 were identified from a prospectively collected database. PWID hospitalised with other infections acted as a novel comparison group. Outcomes were all-cause mortality, cause of death, relapse, recurrence and re-operation.

Results

There were 105 episodes of IE in 92 PWID and 112 episodes of other infections in 107 PWID in whom IE was suspected but rejected. Survival at 30 days for the IE group was 85% and 30-day survival following surgery was 96%. The most common pathogens were *Staphylococcus* spp. (60%) and *Streptococcus* spp. (30%). The surgical intervention rate was 47%. Survival for the IE group at 1, 3, 5 and 10 years was 74%, 63%, 58% and 44%, respectively. This was significantly lower compared with the comparator group of other infections in PWID (p=0.0002). Mortality was higher in patients who required surgery compared to those who did not (HR 1.8, 0.95-3.3). The commonest cause of death was infection (66%), usually a further episode of IE (55%).

Conclusions

Whilst early survival was good, long-term life-expectancy was low. This was attributable to ongoing infection risk, rather than other factors known to affect prognosis in PWID. Surgery conferred no long-term survival advantage. More efforts are needed to reduce re-infection risk following an episode of IE in PWID.

List of abbreviations

IE – infective endocarditis

IVDU – intravenous drug use

PWID – people who infect drugs

UK – United Kingdom

qSOFA – quick Sepsis Related Organ Failure Assessment

mmHg – millimetres of mercury

spp. – species pluralis

Manuscript text

Background

The incidence of infective endocarditis (IE) is rising globally and in developed countries acquired valve disease, valve prostheses, vascular instrumentation and intravenous drug use (IVDU) are the leading causes [1-4]. IVDU is a predisposition for IE, with an incidence 50-100 times higher in people who inject drugs (PWID) [5-7]. American and European guidelines define heart failure, uncontrolled infection, large vegetation size and embolization as indications for cardiac surgery, which is carried out in approximately half of cases [7-9].

Previous studies of IE in PWID have been heterogenous. Most have been retrospective, had a small size and limited to patients who underwent surgery [10-15]. Studies predating the development of the modified Duke criteria will have had less accurate case identification than more recent series, potentially resulting in erroneous reporting of the surgical intervention rate [10, 12, 14]. Lack of a comparator group [10, 16] or a control group of non-PWID patients [13, 14, 17] are additional limitations. Although reported short-term survival in these studies is similar between the PWID and non-PWID, the latter groups typically are older and have more comorbidities [12, 15]. Few studies have described the long-term outcomes for PWID with IE and none have compared survival rates between those who were or were not operated on.

Important factors relevant to long-term outcomes and the timing of surgery in PWID, that might be of less relevance in non-PWID patients, include non-adherence to prescribed antimicrobial regimens and ongoing behaviours that increase the risk of re-infection [10, 17]. The rate of re-operation in PWID is significantly higher than in non-

PWID [12, 15], which has prompted reflection and commentary on repeating surgery in this patient group [18].

Objectives

We aimed to describe the characteristics, complications and long-term outcomes following an episode of IE for a cohort of PWID presenting over a decade to the Leeds Teaching Hospitals NHS Trust. The principle focus was the effect of surgery on long-term outcomes. We also studied the re-infection rates and the causes of death and how these findings might influence decision making regarding surgery for recurrent infection. Finally, we compared outcomes in PWID who had confirmed IE (PWID-IE) with PWID hospitalised for other infections (PWID-no-IE) during the same time period. We hypothesised this would give a meaningful comparison group to determine the extent to which an episode of IE affects survival beyond other factors known to determine prognosis in PWID.

Methods

Study design

Observational cohort study, designed and reported using the STROBE statement [19].

Ethics

The study protocol was submitted to the Research and Innovation Department at our institution. It was regarded as a service evaluation and therefore did not require specific ethical approval or patient consent, providing that usual data protection was in place. Only members of the clinical team had access to routinely collected data, which were anonymised at the point of analysis.

Funding

No specific funding was used for the completion of this study.

Setting

This study was undertaken at the Leeds Teaching Hospitals NHS Trust which is a tertiary referral centre for cardiology and cardiac surgery. Our centre comprises of two large teaching hospitals with over two thousand inpatient beds and a catchment area for referrals of over 3.5 million people of rural, urban and sub-urban demographics.

Participants

Consecutive patients aged 18 years or over reviewed between 01/01/2006 and 31/12/2016 were eligible to be included prospectively in a database designed for service evaluation of IE management. Inclusion was dependent on the modified Duke criteria [7]; we required episodes to be either Duke definite, or Duke possible and treated for IE with IVDU within 90 days. PWID referred to the IE team for assessment but were either Duke excluded or Duke possible and not treated for IE were regarded as a comparator group.

Variables and data sources

The data for each patient were confirmed with reference to the written medical record as well as local electronic data systems. The variables collected included patient demographics, date of episode, severity of illness at presentation, affected structure(s), microbiology and complications. These variables and IVDU status were recorded routinely for all patients reviewed for suspected IE. Complications of IE were

defined as heart failure, emboli, failure of medical therapy or intracardiac abscess. Those with indications for surgery were referred to the multidisciplinary heart team. Decisions to operate were made by consensus and on an individual basis, with indications for surgery defined by international guidelines. The timing, indication(s) for and type of operation(s) were recorded. Emergency surgery was surgery within 24 hours, urgent within the index episode and elective following discharge from hospital.

Outcomes

The primary outcomes were all-cause mortality at 30-days following completion of antimicrobial therapy, 30-days following surgery and at 1, 3, 5 and 10 years. Patients were followed up until death or one year following study completion. Secondary outcomes were IE-related mortality, relapse, recurrence and a second operation. Outcome data were obtained from the Leeds Teaching Hospitals NHS Trust electronic health record, which updates mortality events daily directly from the UK Office of National Statistics (ONS) database. Dates and causes of death were confirmed from the hospital medical records. In those without available electronic data, applications were made to the local Coroner's office to obtain details of the recorded cause of death.

Statistical analysis

A complete dataset was available for all variables except the severity of illness score and cause of death. To assess the impact of missing values of the severity of illness score, sensitivity analysis was performed using three regression models. In the first model, we performed the analysis using complete cases only. For the second model

missing values were assigned zero points, and in the third they were assigned one point.

Continuous variables are expressed as mean ± standard deviation and discrete values are presented as numbers and percentages. Unadjusted survival analysis is displayed by Kaplan-Meier plot with survival differences determined by log-rank alongside 95% confidence intervals for comparisons between: PWID-IE and PWID-no-IE, PWID operated on and those managed conservative, and PWID who eceived mechanical valve prostheses compared to bioprosthetic valves. A Cox regression model was performed to determine the effects of surgery on all-cause mortality and was adjusted for important covariables. The pre-specified confounding factors were age, sex, severity of illness at presentation, left-sided IE and infection with *S. aureus*. In all analyses a *p* value of <0.05 was regarded as statistically significant.

Definitions

An episode was considered to be a discrete inpatient period of treatment for infection. Microbial cause of IE was determined by blood culture and/or by analysis of tissue from excised valves obtained at operation. For the purpose of analysis, the aetiology of infection was grouped as: *Staphylococcus aureus,* coagulase negative staphylococci, beta-haemolytic streptococci, oral streptococci, *Streptococcus anginosus* group, coliforms, enterococci, pseudomonads, *Candida*, 'other' and culture negative.

Severity of illness was stratified by quick Sepsis Related Organ Failure Assessment (qSOFA) score, which has been validated in prospective studies and shown to be of

greater prognostic accuracy than systemic inflammatory response syndrome or severe sepsis criteria[20]. Heart failure was defined as the presence of clinically or haemodynamically significant regurgitation, large vegetations causing haemodynamic compromise or perforation.

The earliest episode during the study period was regarded as the index episode. Relapse was IE caused by the same microorganism within a year, recurrence was re-infection beyond one year, or infection with different microorganism. The start of an episode was defined as the date of the first positive blood culture or echocardiogram. The 30-day mortality and 30-day surgical mortality were any death within 30-days of completion or therapy and operation respectively.

Results

Participants

199 PWID were assessed by the IE team. 105 episodes of IE occurred in 92 patients; 92 were Duke criteria definite and 13 Duke criteria possible. 112 episodes of other infections occurred in 107 PWID not treated for IE; 111 were Duke excluded and 1 was Duke possible. The final diagnoses in PWID-no-IE were infected deep venous thrombosis (41), skin or soft tissue infection (26), osteomyelitis (9), septic arthritis (6), septic pulmonary emboli or lung abscess (5), central line infection (4), pneumonia (4), urinary tract infection (2), pericarditis (2) and cerebral abscess (1). Whilst there was no conclusive evidence of infection in 12 episodes.

Patient demographics

Of the 92 PWID-IE, 65 (71%) were male, the median age was 36 years with no difference between male and females. The number of IE episodes varied considerably from year-to-year with no clear trend. The median age increased throughout the study period from 29 years to 42 years (Table 1). Of the 107 PWID-no-IE 69 were male (64%) and the median age was 36 years.

Microbiology

The microorganisms causing IE were predominantly *Staphylococcus* species, whilst *Streptococcus* species affected the majority of the remaining cases. There was a similar distribution of infections in PWID-no-IE (table 2).

Affected structures

Left sided structures were involved in 72 (64%) episodes, whilst right sided involvement occurred in 40 (36%) episodes; in 15 episodes more than one structure was affected. Prosthetic valve infection accounted for 12 episodes. The mitral valve was most commonly affected (44), followed by aortic (38), tricuspid (38) and pulmonary (2). A pacemaker lead infection occurred in one patient and was treated by extraction.

Complications

The most common complications were heart failure in 51 (49%) episodes, stroke in 16 (15%), pulmonary emboli in 20 (19%), splenic emboli in 11 (11%), other emboli in 8 (7%) episodes and aortic root abscess in 2 (2%) episodes. Thrombo-embolism to other sites included renal, mesenteric, upper and lower limb arteries. There was one instance of endophthalmitis.

Surgery

Surgery was undertaken in 49 (47%) episodes for 48 patients. There were no significant differences in age, sex, *S. aureus* infection or severity of illness score between those requiring surgery and those who did not, but operated patients were significantly more likely to have left sided infection (Table 1). Heart failure was the primary indication for surgery in 33 episodes and a secondary indication in four (total 76%). Aortic root abscess was the indication in one episode (1%), embolization being the primary indication in 14 and secondary indication in 15 episodes (total 28%) and infection with fungi was the indication for one (1%).

Emergent surgery was performed in five episodes (10%). Surgery was performed on an urgently in 42 episodes (86%) and electively following discharge for two patients (4%). Bioprosthetic valve replacement for left-sided IE was the commonest surgical procedure (Table 3). There was one attempt at pulmonary valve replacement which was abandoned on technical grounds owing to inflammatory adhesions. Combined surgical procedures were undertaken for nine patients. During the study period only one patient underwent repeat surgery due to late recurrence of *S. epidermidis* affecting a bioprosthetic mitral valve.

Major complications occurred in 29 episodes in which surgery was not undertaken, in 21 episodes there was no class I indication for surgery. In eight episodes there was a class I indication, however patients were too unwell to undergo an operation and did not survive.

Relapses and recurrences

Relapse occurred in three (3%) patients, one patient had two episodes of relapse, and all were caused by early re-infection with *S. aureus*. Recurrence occurred in 12 (13%) patients, one of whom had two episodes of recurrence. In sub-group analysis of those with recurrence, eight (75%) were not alive at follow-up, three deaths occurred within 30 days, and IE-related mortality was documented in 6 cases.

Survival

The 30-day mortality was 16 (15%) and the 30-day surgical mortality was 4 (8.5%). During a median follow-up of 3.4 years, there were a total of 42 deaths (46%). The long-term survival for PWID-IE and PWID-no-IE are shown in table 4. In Kaplan-Meier analysis, survival was significantly lower in PWID-IE compared to PWID-no-IE (p=0.0002) (Figure 1). There was no statistically significant difference in survival in the operated group compared to the non-operated group (p=0.067) (Figure 2), and this was true when adjusted for the pre-specified covariates (Table 5) and when surgery was analysed as a time-dependent variable (Supplementary table 1). There was no association between choice of bioprosthetic or mechanical valve replacement and survival (p=0.12) (Figure 3).

Additionally, a large proportion of both groups failed to reach predicted life-expectancy. Taking the median ages of the males (36 years) and females (34 years) in this study, then the expected life expectancies for each sex are 73·7 years and 74·2 years, respectively referring to data published by the UK ONS [21] (Supplementary table 2).

Causes of death

Medical certificates for cause of death were available for 38 patients (90%). 21 deaths were reported to be due to an episode of IE. Drug overdose was the recorded cause of death for six patients, and in four patients death was due to another infection. In two patients cardiac failure was the documented cause of death and for one patient the cause of death was unascertained.

Conclusions

The principle finding of this study was that a low 30-day mortality relative to IE mortality in general did not translate into favourable long-term outcomes in a cohort of PWID-IE. By analysis of predicted survival from the ONS it is evident that the total number of lost years-of-life is very high.

Our findings reinforce earlier reports of high early survival followed by poor long-term outcomes in PWID-IE. In a series of 280 PWID-IE patients, Arbulu et al. reported a mortality rate of 21% during an unspecified period of follow-up[16]. In a cohort of 29 PWID undergoing surgery for IE, Osterdal et al. reported death in 13 (45%) patients during a median follow-up period of 22 (0-84) months, with reported 2 and 5-year survival rates of 79 and 59%, respectively[10]. Rabkin et al. reported survival in the PWID group of 91%, 78%, 47% and 41% at 30 days, 1-year, 5-years and 10-years[14]. In a comparison of non-PWID patients with PWID patients, Thalme et al. reported that all five PWID who underwent cardiac surgery had died after 3.3 years[13].

All patients in our cohort who underwent surgery had a class I indication and some had multiple indications, so there is no suggestion from this work that surgery could

have been withheld from these patients. Surgical correction of heart failure caused by significantly regurgitant heart valves in the setting of IE is recommended on prognostic grounds in appropriately selected patients[22]. The lack of a survival benefit in those PWID that underwent surgery may be due to differences in disease severity; the operated cohort had worse valvular dysfunction, heart failure or had uncontrolled infection. However, in the absence of trials, a survival benefit of surgery in this group should not be assumed. Our cause-of-death analysis provides possible explanations for the high mortality, whichever treatment pathway is chosen with the unique finding that death in half the patients was caused by a further episode of IE. Although recent data have supported the concept of survival benefit from surgery, their cohort had more right-sided disease, and a lower surgical intervention rate than in our series [23].

All patients were offered support by the local drug dependency service. This comprised a visit from a designated key worker and where indicated, prescription of medications for opioid use disorder. Despite this, similar to other reports, our cohort had a high rate of return to drug use and re-infection, and only 44% of patients were alive at 10 years. Arbulu et al. reported that all of the 23 late deaths they observed were associated with continued IVDU, whereas all 70 patients who ceased injecting drugs survived[16]. Rabkin et al. reported eight cases of re-infection in the PWID sub-group, which was higher than the non-PWID group (13% compared to 2%). Osterdal et al. found on-going IVDU rates of 70% and 44% in patients undergoing a first or second operation, respectively[10]. Kim et al. compared PWID with non-PWID and found that despite a similar long-term survival, rate of re-infection were much higher in PWID (36% compared to 4%, $p<0{\cdot}001$)[12]. In the largest contemporary analysis

of PWID with IE, Rodger et al. demonstrated that drug addiction services were one factor which helped improve outcomes[23].

Our comparator group (PWID-no-IE) had better survival than PWID-IE (Figure 1), implying that cardiac infection has a negative impact on survival in PWID beyond infection elsewhere. It seems likely that damaged native heart valves, or indwelling prosthetic material poses increased risk of re-infection in the setting of continued IVDU. None of the international guidelines make specific recommendations for cardiac surgery in PWID. In clinical practice, we often encounter the difficult issue that the threshold for operation (and especially repeat operations) could be higher in PWID-IE than non-PWID in whom the re-infection rate is lower, however we do not feel that this work supports withholding surgery from PWID. Survival was not affected by the choice or mechanical or bioprosthetic valve, although the numbers at risk were small. The lack of requirement for anticoagulation is relevant in this patient group whose younger age would usually favour the choice or more reliable mechanical valve replacements.

Study limitations

We prospectively collected data on factors that are known to affect outcomes in IE but it is likely that other confounding factors were present but unmeasured. Another limitation of this study is the single centre setting, meaning the generalisability is uncertain. However, our study represents a large contemporary case series of IVDU related IE, reports outcomes from all affected valves, and includes patients managed both medically and surgically. The preponderance of left-sided disease may reflect inclusion bias, as a cardiac surgery referral centre will receive more patients with left-

sided infection complicated by heart failure or embolic risk, but is consistent with other recent studies [10, 12, 14]. The high rate of IE-related mortality suggests that the relapse and recurrence rates reported here may have underestimated the rate of re-infection. A major limitation of our project was that we did not collect detailed data on specific drug addiction services offered to PWID or their uptake.

Key findings

Following an episode of IE, the long-term survival for patients with predisposing IVDU was poor. Whilst surgery can redress haemodynamic and embolic complications, it is only a part of the holistic approach necessary to manage this challenging patient group. A review of the approach to surgical treatment in these individuals and the support and harm reduction input these patients receive may be necessary especially in those who persist with IVDU and develop re-infection, requiring a second operation [24].

Notes

Declaration of interests

JS participates in research with funding from Pfizer and Merck Sharpe and Dohme. KKW receives consulting fees from Medtronic, Bayer and Novartis; receives speaking fees from Medtronic, Bayer, Novartis, Napp and Abbott; and holds an unrestricted research grant from Medtronic. There are no conflict of interests to declare for the other authors.

Authorship

SS, WB and JS researched the topic and devised the study.

JS, SS, WB and RG collected the data and undertook primary statistical analysis.

SS and WB produced the first draft of the manuscript.

All other co-authors contributed to manuscript preparation.

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The research took place at the Leeds Teaching Hospitals NHS Trust and the Leeds NIHR Clinical Research Facility.

Table 1.

Title: Characteristics of patients with infective endocarditis stratified by surgery.

Caption: Baseline characteristics are similar in those operated and non-operated with the exception of left-sided infection.

Characteristic	All patients n = 92	Not operated n=47	Operated n=45	P-value
Age (years), mean (sd)	36.7 (8.4)	36.1 (8.7)	37.4 (8.2)	0.49
Male	65 (71)	33 (70)	32 (71)	1.0
S. aureus	53 (58)	30 (64)	23 (51)	0.31
Side				
Left-side	49 (53)	20 (43)	29 (64)	
Right-side	30 (33)	24 (51)	6 (13)	**<0.001**
Both	13 (14)	3 (6)	10 (22)	
qSOFA >= 2	12 (16)	7 (18)	5 (14)	0.87

Table 2.

Title: Microorganisms causing infection in PWID-IE and PWID-no-IE

Caption: *Staphylococcus* and *Streptococcus* species caused the majority of infections in PWID.

Microorganisms	PWID-IE (n)	PWID-no-IE (n)
S. aureus	63	39
Coagulase-negative *Staphylococcus*	2	3
Beta-haemolytic *Streptococci*	19	16
Oral *Streptococci*	9	6
Streptococcus anginosus	3	6
Enterococcus spp.	8	2
Coliforms	0	3
Candida spp.	2	0
Pseudomonads	1	1
Other	1	3
Culture negative	7	41

Table 3.

Title: Surgical procedures by type and affected structure

Caption: Bioprosthetic valve replacement for left-sided IE was the commonest surgical procedure.

Surgical procedure	n
Aortic valve replacement	24
Bioprosthetic	18
Mechanical	6
Mitral valve replacement	19
Bioprosthetic	11
Mechanical	9
Tricuspid valve replacement	8
Pulmonary valve replacement	1
Aortic valve repair	1
Mitral valve repair	5

Table 4.

Title: Overall survival and survival in patients stratified by surgery with 95% confidence intervals.

Caption: Survival was reduced in the operated group compared to the non-operated group. Survival was reduced in patients with endocarditis compared to controls.

	Kaplan-Meier survival rate (95% CI)			
	Endocarditis	Endocarditis operated	Endocarditis not operated	Controls
1 year	73.9 (65.5-83.5)	68.9 (56.6-83.8)	78.7 (67.9-91.3)	91.0 (85.6-96.8)
3 years	62.7 (53.3-73.8)	53.7 (40.5-71.1)	71.5 (59.4-86.0)	86.4 (79.8-93.6)
5 years	58.3 (48.6-70.0)	47.9 (34.7-66.1)	68.5 (55.9-83.9)	83.5 (76.1-91.6)
10 years	43.8 (32.0-59.9)	33.0 (18.4-59.1)	53.2 (36.8-77.1)	70.0 (59.6-82.3)

434 **Table 5.**

435 Title: Cox regression analysis for the association between operation and survival
436 adjusted for important clinical covariables.

437 Caption: In univariate analysis and when adjusted for important clinical covariables,
438 surgery is not associated with a favourable prognosis.

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	Mortality, hazard ratio (95% CI)			
	Univariable model n=92	Multivariable model 1* n=73	Multivariable model 2* n=92	Multivariable model 3* n=92
Surgery (Yes vs No)	1.8 (0.95-3.3)	1.4 (0.68-2.7)	1.3 (0.68-2.6)	1.7 (0.75-3.8)
Age		1.0 (0.96-1.1)	1.0 (0.98-1.1)	1.1 (1.0-1.1)
Sex (Male vs Female)		0.98 (0.48-2.0)	1.0 (0.50-2.1)	0.67 (0.30-1.5)
S. aureus (Yes vs No)		0.73 (0.38-1.4)	0.81 (0.43-1.5)	0.43 (0.20-1.9)
Side				
Left-side		1	1	1
Right-side		0.44 (0.18-1.1)	0.46 (0.19-1.1)	0.52 (0.19-1.4)
Both		0.67 (0.24-1.8)	0.70 (0.25-1.9)	0.20 (0.04-0.95)
qSOFA				
<2		1	1	1
>=2		1.9 (0.74-5.0)	1.5 (0.73-2.9)	2.7 (0.95-7.4)

Model 1: complete case for qSOFA

Model 2: altered mentation, systolic blood pressure <= 100, respiratory rate >= 22 were set to 0 if unknown

Model 3: altered mentation, systolic blood pressure <= 100, respiratory rate >= 22 were set to 1 if unknown

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Supplementary table 1.

Title: Cox regression analysis for the association between operation and survival adjusted for important clinical covariables. Surgery was coded as time-dependent variable where the date of operation was taken into account in the Cox model.

Caption: Survival was not associated with operation in univariate or multivariable analysis.

	Mortality, hazard ratio (95% CI)			
	Univariable model n=92	Multivariable model 1* n=73	Multivariable model 2* n=92	Multivariable model 3* n=92
Surgery (Yes vs No)	1.64 (0.91-3.01)	1.29 (0.61-2.65)	1.22 (0.59-2.32)	1.58 (0.71-3.47)
Age		1.0 (0.98-1.04)	1.0 (0.98-1.05)	1.04 (1.0-1.08)
Sex (Male vs Female)		1.08 (0.49-1.67)	1.09 (0.51-1.67)	0.65 (0.31-1.29)
S. aureus (Yes vs No)		0.77 (0.24-1.30)	0.82 (0.31-1.33)	0.46 (0.22-1.12)
Side				
Left-side		1	1	1
Right-side		0.31 (0.18-1.04)	0.31 (0.19-1.03)	0.30 (0.11-1.12)
Both		0.63 (0.24-1.46)	0.64 (0.23-1.45)	0.15 (0.01-1.63)
qSOFA				
<2		1	1	1
>=2		1.63 (0.88-2.39)	1.50 (0.95-2.04)	2.21 (1.42-2.99)

Model 1: complete case for qSOFA

Model 2: altered mentation, systolic blood pressure <= 100, respiratory rate >= 22 were set to 0 if unknown

Model 3: altered mentation, systolic blood pressure <= 100, respiratory rate >= 22 were set to 1 if unknown

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Supplementary table 2.

Title: Life expectancy with 95% confidence interval for IVDU patients with IE stratified by surgery and sex.

Caption: The life expectancy of a healthy 36 year-old male is an additional 44.3 years and of a healthy 34 year-old female is 49.6 years. In comparison, the life expectancy for IVDU patients following an episode of endocarditis is substantially less, particularly in the operated group.

			Life expectancy after treatment (years)	
		10-year mortality rate (%)	for a 36-year old male	for a 34-year old female
Male	Surgery	80 (68,92)	6.2 (3.9, 8.8)	-
	No surgery	49 (43,55)	14.4 (12.4,16.9)	-
	Overall	60 (52,68)	10.7 (8.7,13.4)	-
Female	Surgery	57 (46,67)	-	11.8 (9.1,15.7)
	No surgery	36 (30,42)	-	20.6 (17.5,24.1)
	Overall	46 (38,54)	-	15.6 (12.7,19.4)

Figure titles and legends

Figure 1.

Title: Kaplan-Meier plot of the survival of PWID in cases with confirmed infective endocarditis compared to PWID with other infections.

Caption: Survival was significantly reduced following an episode of infective endocarditis compared to PWID with other infections (p=0.0002).

Figure 2.

Title: Kaplan-Meier plot of the survival of PWID in cases with confirmed infective endocarditis, stratified by operated or not operated.

Caption: There was a trend towards reduced survival in the operated group (p=0.067)

Figure 3.

Title: Kaplan-Meier plot of the survival following surgery for infective endocarditis in those receiving bioprosthetic or mechanical valve replacements.

Caption: There is no significant difference in survival between those receiving mechanical or bioprosthetic valve replacement.

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