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THERAPIES

HEADING: Pharmacovigilance

Bacterial infections in people who inject psychoactive substances: an observational study in a French university hospital

Bacterial infections in injection drug users

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Summary

Aim of the study.- To describe bacterial infections in injection drug users (IDUs) hospitalized at Montpellier University Hospital, France, and to identify factors that might influence the development of local or systemic infections. *Methods*.- This cross-sectional observational monocentric study prospectively included bacterial infections in IDUs hospitalized at Montpellier University Hospital between 2012 and 2018. Types of infection (local or systemic) were described and compared to identify specific features (injection practices). *Results*.- The study included 144 bacterial infections (56% of local infections and 44% of systemic infections) concerning 117 IDUs. The most common infection types were abscesses (50%), skin and soft tissue infections (33%), bacteremia/sepsis (20%), endocarditis (17%), and bone and joint infections (16%). Patients were mainly men (n = 94; 80%), and the median age was 40 years [IQR_{25-75}: 34-47]. Four deaths related to systemic infection were reported. The most frequent injected substances were cocaine, opioid maintenance treatments (OMT), and opioids. According to the multivariate analysis, factors associated with the occurrence of systemic infections were number of injection (OR 2.59 [1.07-6.27]; $p = 0.034$) and injection of at least one opioid (OR 3.52 [1.28-9.72]; $p = 0.015$). *Conclusion*.- Different types of bacterial infections, local or systemic, are observed in IDUs. Skin infections are quite common, but other infection types also are reported, with sometimes serious consequences. It is already known that injection practices are contributing factors in infection development, but the type of injected psychoactive substance(s) also may have an influence.

KEYWORDS

Substance abuse; Intravenous; Bacterial infections; Harm reduction; Substance-related disorders

Abbreviations

ELSA: *Équipe de liaison et de soins en addictologie* (local addiction management and liaison team)

HCV: hepatitis C virus

HIV: human immunodeficiency virus

IDUs: injection drug users

IE: infective endocarditis

OMT: opioid maintenance therapy

PS: psychoactive substances

SSTI: skin and soft tissue infection

USA: United States of America

Introduction*

Injection drug users (IDUs) are at high risk of potentially life-threatening bacterial infections related to injection of psychoactive substances (PS) [1-2]. These bacterial infections carry a major risk of hospitalization, morbidity and mortality, and are associated with a significant health cost [3-4]. Published data show that the rate of several bacterial infection types has been increasing in different areas in the United States of America (USA) in the mid-2010s [5]. Similarly, since 2013, in the United Kingdom, the number of injection-related bacterial infections in IDUs has increased [6]. Few French studies and case reports have examined bacterial infections in IDUs, but none of them (to our knowledge) included large national data on bacterial infections in people who inject PS [7]. Much research has focused on the risk of transmission of blood-borne viruses, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV), in this population, conversely less is known about bacterial infections linked to PS injection.

Many different bacterial infection types have been linked to PS injection, such as abscess, skin and soft tissue infection (SSTI), sepsis, infective endocarditis (IE), bone and joint infections, pneumonia, with frequency and severity differences [8-11]. SSTI is a leading cause of emergency department visits among IDUs [12]. The occurrence of bacterial infections in IDUs has been associated with several factors, such as poor hygiene, unsafe injection practices, frequent injections, and non-adherence to medical treatment [13].

The main aim of this study was to describe the characteristics of bacterial infections in IDUs hospitalized at Montpellier University Hospital, France, from 2012 to 2018. The second aim was to identify potential factors associated with the risk of local or systemic infections in IDUs.

Methods

Study design

This cross-sectional observational study included all cases of bacterial infections in IDUs hospitalized at Montpellier University Hospital, France, from January 2012 to December 2018. All

injection routes were included (intravenous, subcutaneous, intramuscular, and intra-arterial). Fungal and viral infections or bacterial infections in the absence of PS injection were excluded.

To improve data collection, two complementary sources were used: i) spontaneous reports to the regional addictovigilance centre (required by French regulation to monitor abuse and misuse of PS) and ii) local collaboration with several hospital departments (department of infectious diseases and department of addictology) and the local addiction management and liaison team (ELSA), to collect more exhaustive and efficient data (Fig. 1). The regional addictovigilance centre is a member of the French Addictovigilance Network that was established in 1990 to monitor the potential for PS abuse and dependence (with the exclusion of tobacco and alcohol), and to provide information on the risk of addiction and advice for public health decision making, under the supervision of the French National Agency for Medicines and Health Products Safety [14]. This surveillance system is principally based on spontaneous reporting by healthcare professionals and patients that is regulated by law [15-16]. ELSA main mission is to advise and assist caregivers on addiction, screening, diagnosis and treatment of drug-related diseases [17]. They are an interface between hospital departments and support structures for addiction management. This innovative process of data collection was put in place to optimize the exhaustiveness of data collection by creating a reporting system that is closer to hospitalized IDUs. Cases and data were identified and collected prospectively.

Type of data collected

Several data were collected from the spontaneous reports to the addictovigilance center and from the patient electronic health record, such as demographic data (age, sex), medical history (past history of bacterial infections, HIV and HCV status), injected PS, injection practice (frequency, location, and route), infection diagnosis, bacterial analysis, treatments, and infection course. Infections were categorized in two groups: local and systemic. Local infections were defined as infections localized in an area that did not spread (e.g. skin abscess and localized SSTI). Systemic infections were defined as infections that spread from the injection site (e.g. sepsis and IE). The term “abscess” defined several types of abscesses (e.g. skin, deep, or invasive abscess).

Moreover, the ELSA team asked all IDUs hospitalized for a bacterial infection to fill in a questionnaire on hygiene habits as part of their addiction management. Participants were free not to respond. The questionnaire included questions on whether they disinfected the skin at the injection

site, on whether they washed their hands before injection, and the disinfection products used, and on their injection habits (alternative injection site, sterilized needle, filter, etc.).

Concerning PS use, data were categorized as: i) individual PS and ii) pharmacological groups. Opioid maintenance treatments (OMT) were methadone and high-dose buprenorphine. Opioids were prescription opioids such as morphine, oxycodone, fentanyl and the illicit opioid substance heroin. Stimulants were cocaine, amphetamines, synthetic cathinones and methylphenidate [18].

The study protocol was approved by the local ethics committee (*Comité d'éthique régional):* IRB-MTP_2020_09_202000587.

Statistical analysis

Qualitative parameters (medical history, type of infections, bacterial analysis, treatments, injection practices, and answers to the hygiene questionnaire) were described with frequencies and percentages. Quantitative parameters (age) were described with median and first and third quartiles.

As one patient could have had more than one bacterial infection episode that required hospitalization during the study period (2012-2018), each infection episode was defined as a statistical unit.

Injection practices between local and systemic infections were compared using the Chi-square test or Fisher exact test (when Chi-square test were not appropriate). A student test was performed to compare ages between local and systemic groups. A multivariate analysis using logistic regression was performed using ages as continuous variables. Categorical variables with the most favorable outcome and taken as reference level were: injection of an opioid, intravenous injection and number of different PSs injected. Odds-ratio (OR) and their confidence intervals (CI) were calculated. A p-value <0.05 was considered significant for all the statistical analyses performed.

All the analyses were conducted using the SAS software (SAS Enterprise Guide 8.2, SAS Institute Inc., Cary, USA).

Results

Demographic data and medical history

In total, data on 144 bacterial infections related to PS injection in 117 IDUs were collected. The main epidemiological features are summarized in Table 1. Patients were mainly men (80.3%) with a median age of 40 years (IQR_{25-75}: 34-47). Sixty-five patients (54.2%) had a lifetime history of bacterial infections, and 35 (31.3%) reported a bacterial infection in the year before the current episode. During the study period, 96 patients (82.1%), 16 (13.7%), 4 (3.4%), and 1 (0.9%) had one, two, three and four bacterial infection episodes, respectively.

Description of the bacterial infections

Among the 144 bacterial infections, 80 (55.6%) were local infections and 64 (44.4%) systemic infections. Some IDUs presented concomitantly several infection types due to the spread of bacteria (e.g. an IE with a local abscess). Therefore, in the systemic infection group, the medical record of 20 patients mentioned a systemic infection with local clinical signs. For the analysis, these 20 cases were considered only as systemic infections, to comply with the choice of infection location as statistical unit (see Methods), and considering that the infection had spread. The number (local/systemic) of bacterial infections per year was 20 (8/12) in 2012, 25 (19/6) in 2013, 18 (10/8) in 2014, 20 (12/8) in 2015, 20 (13/7) in 2016, 18 (10/8) in 2017, and 23 (8/15) in 2018. This represented 9.1/100,000 hospitalizations in 2012, 11.2/100,000 in 2013, 8.0/100,000 in 2014, 8.7/100,000 in 2015, 8.5/100,000 in 2016, 7.5/100,000 in 2017, and 9.8/100,000 in 2018 [19]. The bacterial infection type and characteristics are summarized in Table 2. Abscess was the most common type (n = 72; 50.0%), followed by SSTI (n = 47; 32.6%). Concerning IE (n = 25; 17.4%), 11 were right-sided (tricuspid or pulmonary valve; 46%), 12 were left-sided (aortic or mitral valve, 50%), one was in both sides, and one had an unknown localization. Methicillin-sensitive *Staphylococcus aureus* was the most commonly found bacterium in blood cultures (n = 38/106), and other Gram-positive bacteria in other non-blood samples (n = 40/75). Methicillin-resistant *S.*

aureus was isolated in one blood culture, one bronchoalveolar lavage, and one osteoarticular sample. The infection outcome was favorable in 88% of cases (n = 113/128) at the time of the report. Four patients died due to the infection and one due to another cause. All infection-related deaths occurred in patients with systemic infection.

Injection practices

Table 3 presents the data on the injection practices in the local and systemic infection groups. The intravenous route was reported in 130 infection episodes, and the subcutaneous, intra-arterial and intramuscular route in 5, 4, and 3 episodes, respectively. Subcutaneous injection was reported only by IDUs with local infection events (6.7% vs 0.0%; p = 0.063). The injection of a single drug was reported in 107/142 infections (75.4%), but the percentage was different between groups (85.9% in the local infection vs 62.5% in the systemic infection group, respectively; p = 0.0028). Injection frequency was mainly daily (n = 74/96; 77.1%), without any difference between groups. The most frequently injected PS were stimulants, alone or in combination with another PS (n = 90/142; 63.4%), mostly cocaine (n = 73). Injected opioids were morphine (n = 20) and heroin (n = 9). New psychoactive substances (only synthetic cathinones: mephedrone, n = 3; 3-methylmethcathinone, n = 3) were involved in six bacterial infections, including two in a chemsex context. Comparison by univariate analysis of the injected PS in the two groups (Fig. 2) showed that co-injection of a stimulant with an opioid (17.2% *vs* 3.9%; p = 0.008), or of an opioid alone or in association with other PS (31.3% *vs* 10.3%; p = 0.0018) was more common in the systemic infection group. Conversely, injection of an OMT alone tended to be more frequently reported in the local infection than in the systemic infection group (32.1% *vs* 18.8%; p = 0.0724).

In multivariate analysis adjusted on age (Table 4), two variables were significantly associated with systemic infections: injection of at least one opioid (OR: 3.52 [95% CI: 1.28-9.72]; p = 0.015] and the number of PSs injected (OR: 2.59 [95% CI: 1.07-6.27; p = 0.034]). There was no significant interaction between them. Intravenous injection was not significant (OR: 3.51 [95% CI: 0.41-30.29]; p = 0.254]. The model suitability is good with a concordance rate of 71.7% between predicted probabilities and observed values.

Sixty IDUs (41.7% of 144) filled in the hygiene questionnaire, but often not completely, leading to a high number of missing data (Fig. 3). More than two-thirds of IDUs that responded to the

questionnaire, alternated injection sites, used sterile syringes, sterile cups and risk-reduction packs, such as Steribox®. Conversely, less than four in ten cleaned surfaces before injection or used garrotes. Among the 29 individuals who said that they washed hands before injection, 12 used soap/water and 12 an alcohol-based/antibiotic hand cleanser. Thirty IDUs reported that they disinfected the skin before injection, and four said that they did it sometimes.

Discussion

This cross-sectional observational and multidisciplinary study, from January 2012 to December 2018, collected data on IDUs hospitalized at Montpellier University Hospital due to a bacterial infection with the main aim of describing the characteristics of such bacterial infections. The most common bacterial infections were abscesses, followed by SSTI, bacteremia/sepsis, IE, and bone and joint infections. Patients were mainly adult men with a median age of 40 years. The most frequent injected substances were cocaine, drugs used in OMT, and opioids. Co-injection of more than one substance, particularly a stimulant and an opioid was more frequent in the systemic infection group ($p = 0.008$).

Previous studies also showed that skin infection is one of the most common infectious complications in IDUs. A systemic review found that 6 to 32% of IDUs reported a current SSTI in the previous month, and 7 to 37% in the last 6-12 months before hospitalization [3]. In our study, IE and bone and joint infections also were frequently reported. Bone and joint infections are often underrepresented in published studies, although they display considerable morbidity and mortality [20]. About 16% of patients had a bone and joint infection in our study, a high proportion compared with the other bacterial infection types. In IDUs, IE is a well-known complication of intravenous drug use, with right-side predominance (76% of cases), unlike in non-IDUs where the right valves are involved in 10-13% of cases [21]. In agreement, the rate of right-sided IE was high in our sample (46%).

It has been suggested that the prevalence of complications related to injection drug use varies according to the context [3]. Therefore, we tried to identify some factors that could influence the appearance, spread and severity of bacterial infections. High frequency of injections is already known to promote the appearance of bacterial infections, and many of our patients injected PS at least once per day [2-3]. Yet, the frequency of drug injection was not significantly different in the

systemic and local infection groups. In multivariate analysis, intravenous injection was not associated with systemic infections but almost all IDUs in the study were intravenous drug users. Some previous studies found an association between subcutaneous, intramuscular or even "skin popping" injections and SSTI development [3, 12]. In agreement, in our study, all IDUs who used the subcutaneous route had a local infection (the difference between local and systemic infection was close to significance, $p = 0.063$, certainly due to the small number of IDUs using subcutaneous injections in our study).

The available data indicated that most infections were caused by *S. aureus* and other Gram-positive bacteria that enter the body through the injection sites [22]. These bacteria are common in the human bacterial flora. A study in Vancouver (Canada) found that methicillin-resistant *S. aureus* nasal carriage is increasing among IDUs [23]. However, in our population methicillin-resistant *S. aureus* was detected only in three samples. This difference could be explained by various factors, such as wider bacterial spectrum in our population, different antibiotic selection pressure, or differences in hygiene habits.

Few studies explored the influence of PS on the development, type and course of bacterial infections, possibly because of the large diversity of injection practices and number of PS injected among IDUs. Indeed, it is difficult to determine the involvement of a specific PS in the development of an infection. Moreover, there are also regional specificities in PS abuse patterns. For instance, it has been suggested that the opioid epidemic in the USA might have promoted the occurrence of IEs, skin infections, and joint/bone infections [24]. Similarly, the use of heroin black tar or speedball injection (i.e. the practice of injecting a mixture of an opiate and cocaine) might increase the development of severe bacterial infections. In addition, PS concentration and adulterant content vary in the different regions of the world [2]. In our results, IDUs who combined a stimulant (including cocaine) and an opioid (including morphine) were more likely to be hospitalized for a systemic infection. This is consistent with previous findings showing that speedball injections favor the development of severe bacterial infections, although our patients never explicitly referred to "speedball" injections [2]. Some authors hypothesized that due to its unaesthetic properties, cocaine extravasation is more likely to occur, thus leading to local trauma that favors infections [12]. The PS half-life also could influence the appearance of bacterial infections. Substances with short half-life might lead to an increase of the injection frequency [12]. Moreover in multivariate analysis, injection of an opioid was significantly associated with systemic infections. As some studies have highlighted the immunosuppression potential of opioids, mainly in animals [25], the consumption of opioids might facilitate the development of systemic infections. Our data show that a non-negligible proportion of patients had high-risk injection practices,

especially concerning hygiene. They also suggest that some key prevention messages are more easily implemented (e.g. rotating the injection sites and using sterile syringes) than others (e.g. hand washing and surface cleaning). This probably explains the high infection recurrence rate in our population (history of multiple infections during the study period). Risk reduction strategies in IDUs must be improved to increase behavior changes about injection practices and to limit infection worsening and recurrence. Risk reduction programs represent an important part of the patient care because many IDUs present not only addiction to substance(s), but also to injection. It has been shown that reducing injection intensity decreases the bacterial infection risk in IDUs [26]. Moreover, more research is needed to better understand the specific mechanisms of bacterial infections in IDUs to prevent their occurrence and reduce their severity.

We recognize several limitations in this study. This was a monocentric study and the number of identified cases was limited. Moreover, some infection cases could have been missed due to the data collection system, ELSA team could have not been aware of all bacterial infections cases hospitalized in our university hospital. Also, our collection method may have overlooked IDUs with a bacterial infection who were hospitalized for another condition. In addition, as data collection concerned only patients who were hospitalized due to such bacterial infections, less serious local infections were certainly underrepresented. Concerning the analysis of contributing factors, some groups were too small to draw any conclusions on the influence of some factors in the development of systemic and local bacterial infections. Studying bacterial infections related to PS injection is difficult due to the many confounding factors that might lead to data misinterpretation. The results of this preliminary study create the framework of larger studies that could focus on specific variables.

Conclusion

Injection drug use can lead to many complications among which bacterial infections are common, but not widely studied. Different bacterial infection types are observed in hospitalized IDUs that can have serious outcomes (death), despite medical care. Injection practices are known contributing factors to bacterial infection occurrence, but our data suggest that the type of injected PS also might play a role in the development and possibly severity of the infection. Better understanding the underlying mechanisms could improve infection management and risk reduction strategies.

Authorization of the study

The study protocol was approved by the local ethics committee (*Comité d'éthique régional):* IRB-MTP_2020_09_202000587.

Disclosure of interest

The authors declare that they have no competing interest

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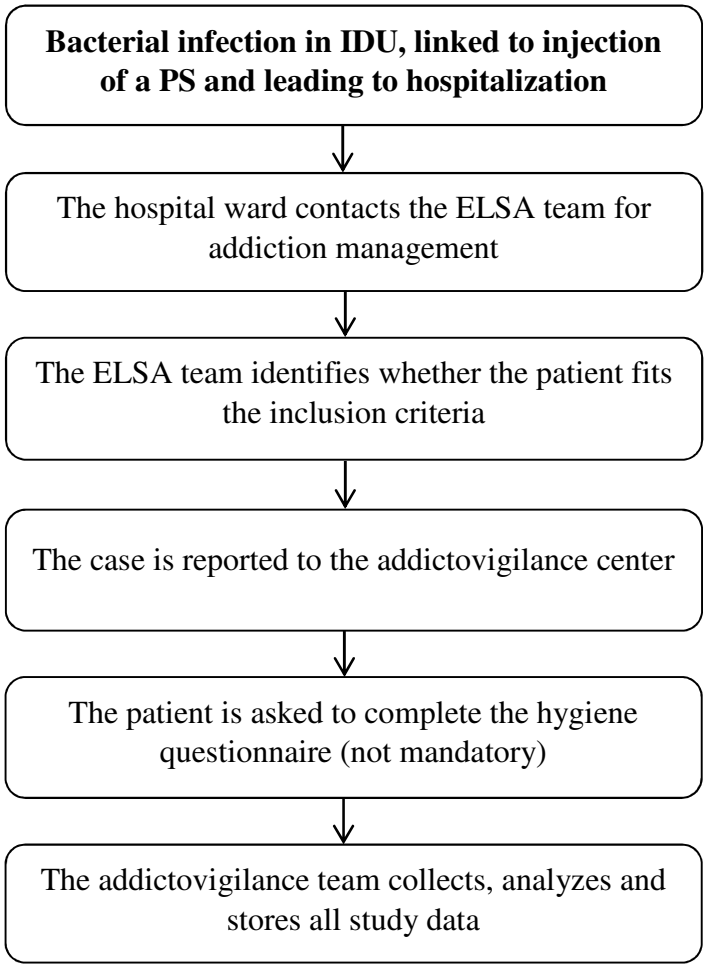

Figure 1. Identification of bacterial infections linked to the injection of psychoactive substances and data collection.

ELSA, local addiction management and liaison team ; IDU: injection drug user; PS: psychoactive substance

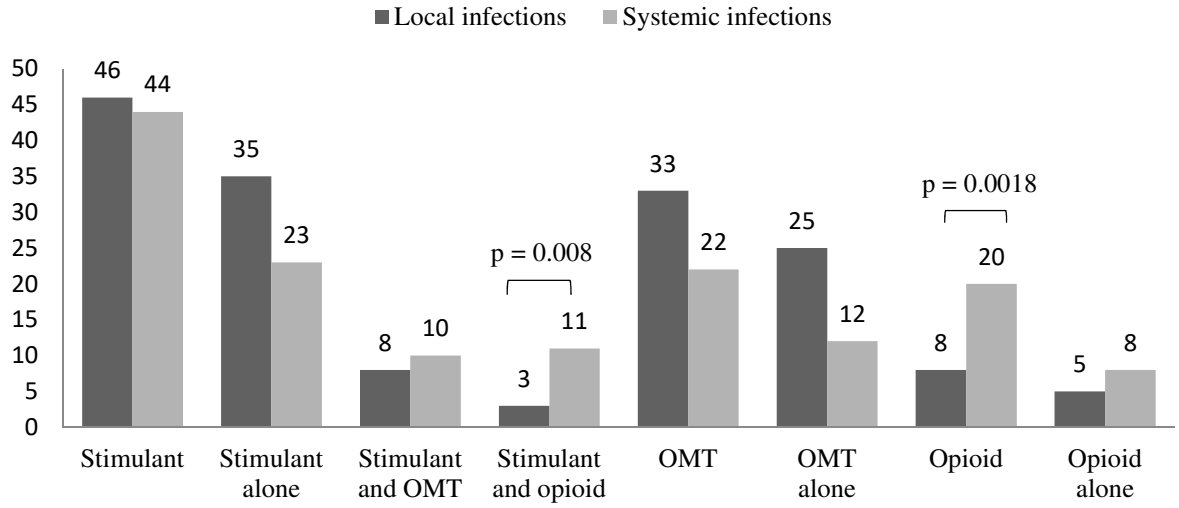

Figure 2. Number and comparison of local and systemic infections according to the injected psychoactive substance - PS(s) - as reported by the patients. Name of PS (e.g. stimulant, opioid, OMT): PS was injected either alone or in combination with another PS; PS alone (e.g. stimulant alone): PS was injected alone; PS and PS (e.g. stimulant and OMT): the two indicated PS were injected together. OMT: opioid maintenance therapy. Stimulant: cocaine, amphetamines, methylphenidate and synthetic cathinones. OMT: buprenorphine and methadone. Opioids: heroin and morphine

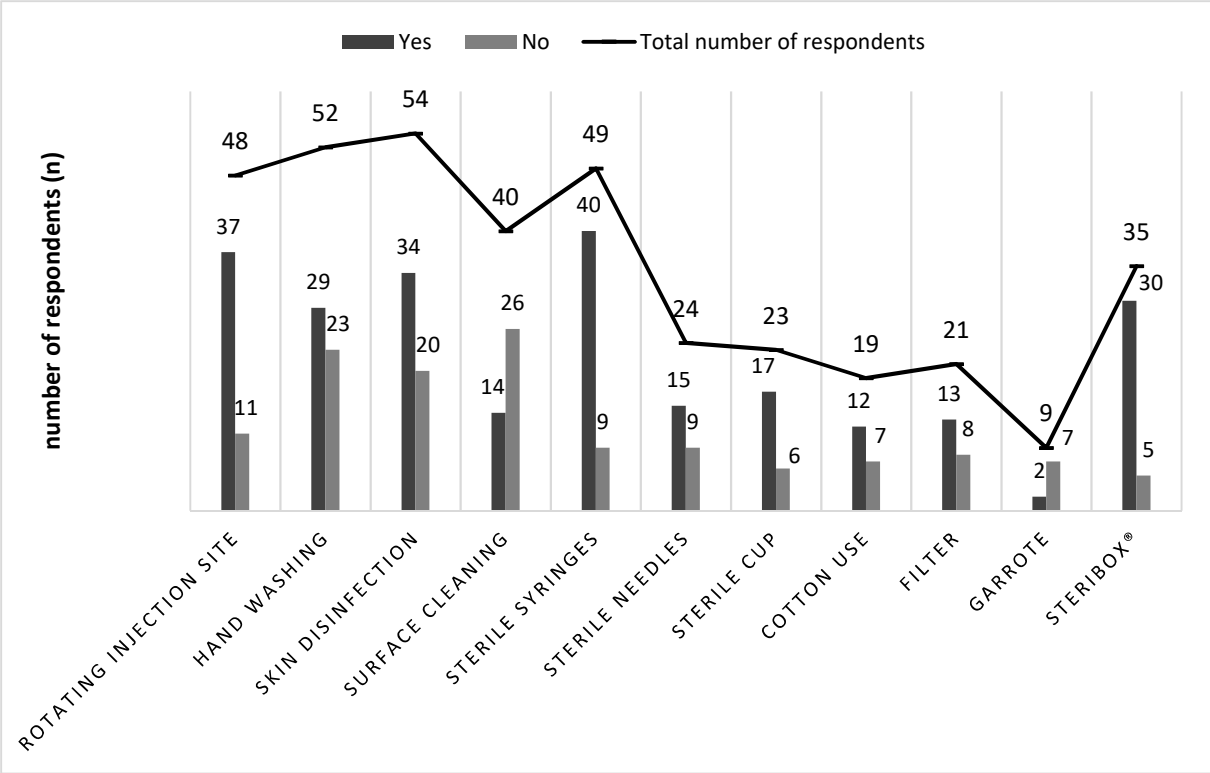

Figure 3. Answers to the hygiene questionnaire by injection drug users hospitalized for bacterial infection (total of 60 questionnaires filled in, but not all of them were complete).

Table 1. Characteristics of the study population (144 bacterial infections).

	n (%)	N[a]
Medical history		
HIV-positive	20 (15.0%)	133
Current hepatitis C infection	66 (49.6%)	133
Previous hepatitis C infection	20 (15.0%)	133
Lifetime history of bacterial infection	65 (54.2%)	120
Bacterial infection(s) in the last year	35 (31.3%)	112
Abscess	11 (44.0%)	25
Skin and soft tissue	6 (24.0%)	25
Osteoarticular	4 (16.0%)	25
Endocarditis	2 (8.0%)	25
Sepsis	2 (8.0%)	25
Psychoactive substance injected		
Opioid maintenance therapy		
Buprenorphine	54 (38.0%)	142
Methadone	1 (0.7%)	142
Opioid		
Morphine	20 (14.1%)	142
Heroin	9 (6.3%)	142
Stimulant		
Cocaine	73 (51.4%)	142
Amphetamines	8 (5.6%)	142
Synthetic cathinones	6 (4.2%)	142
Methylphenidate	8 (5.6%)	142
Anabolic-androgenic steroids	2 (1.4%)	142

[a]N: indicates the total number of patients for whom data were available (missing data are not included in calculation)

HIV: human immunodeficiency virus

Table 2. Main characteristics of the 144 bacterial infections.

	N (%)
Type of infection[a] (n = 144)	
Abscess	72 (50.0%)
Skin and soft tissue	47 (32.6%)
Sepsis/bacteremia	29 (20.1%)
Infective endocarditis	25 (17.4%)
Bone and joint tissue	23 (16.0%)
Pneumonia	6 (4.2%)
Meningitis	3 (2.1%)
Blood culture performed (n = 144)	106 (73.6%)
Positive blood culture	53 (50.0%)
Methicillin-sensitive *Staphylococcus aureus*	38 (35.8%)
Methicillin-resistant *Staphylococcus aureus*	1 (1.0%)
Other Gram-positive bacterium	17 (16.0%)
Gram-negative bacterium	2 (1.9%)
Other samples analyzed[b] (n = 144)	75 (53.6%)
Methicillin-sensitive *Staphylococcus aureus*	33 (44.0%)
Methicillin-resistant *Staphylococcus aureus*	2 (2.7%)
Other Gram-positive bacterium	40 (53.3%)
Gram-negative bacterium	16 (21.3%)
Anaerobic bacterium	8 (10.7%)
Treatments	
Local (nursing, pads, *etc*.) (n = 90)	54 (60.0%)

Surgery (n = 132)	73 (55.3%)
Antibiotic therapy (n = 142)	133 (93.7%)

n, number of infections with available data (missing data not included); [a] Several infection types *per* patient in the same episode; [b]Cell culture, skin, wound, biopsy *etc.*

Table 3. Injection practices.

	Local infections	**Systemic infections**	***p-value***
Injection route[a] (n = 138*)	N = 75	N = 63	
Intravenous	90.7% (68)	98.4% (62)	0.0706
Subcutaneous	6.7% (5)	0.0% (0)	0.0627
Intramuscular	4.0% (3)	0.0% (0)	0.2502
Intra-arterial	2.7% (2)	3.2% (2)	1.0000
Number of different PSs injected (n = 142)	N = 78	N = 64	
One	85.9% (67)	62.5% (40)	0.0028
Two	12.8% (10)	31.3% (20)	
Three	1.3% (1)	6.3% (4)	
Injection frequency (n = 96)	N = 44	N = 52	
Once/several times per day	77.3% (34)	76.9% (40)	0.3462
Once/several times per week	2.3% (1)	9.6% (5)	
Once/several times per month	6.8% (3)	1.9% (1)	
Occasionally or changing	11.4% (5)	11.5% (6)	
One time	2.3% (1)	0.0% (0)	

Injection site (n = 118)	N = 65	N = 53	0.340
Hand	6.2% (4)	7.6% (4)	
Arm	41.5% (27)	30.2% (16)	
Shoulder	1.5% (1)	0.0% (0)	
Neck	1.5% (1)	0.0% (0)	
Foot	3.1% (2)	0.0% (0)	
Leg	15.4% (10)	28.3% (15)	
Variable	30.8% (20)	34.0% (18)	

n, number of infections with available data; [a] Some IDUs used several different routes of injection or injected several different psychoactive substances (PSs).

* For 6 cases of bacterial infection related to injection of psychoactive substance but the type of injection was not specified (intravenous, subcutaneous, etc.).

Table 4. Factors associated with systemic infections (multivariate analysis).

Variables	Local infection (n = 80)		Systemic infection (n = 64)			MODEL[a]	
	mean	**sd**	**mean**	**sd**	**p**	**OR [95% CI]**	**p**
Age	39.0	±9.2	40.7	±8.8	0.263	1.04 [0.99-1.08]	0.088
	n	**%**	**n**	**%**	**p**		
Intravenous injection[b]							
No	7	9.3	1	1.6	0.071	Ref.	0.254
Yes	68	90.7	62	98.4		3.51 [0.41-30.29]	
Injection of an opioid[c]							
No	70	89.7	44	68.7	0.002	Ref.	0.015
Yes	8	10.3	20	31.3		3.52 [1.28-9.72]	
Number of different PSs injected[c]							
1	67	85.9	40	62.5	0.001	Ref.	0.034
≥ 2	11	14.1	24	37.5		2.59 [1.07-6.27]	

[a]Modeled probability is "systemic infection"; [b]missing data: n = 6; [c]missing data: n = 2

CI: confidence interval; OR: odds ratio; PS(s): psychoactive substances