

Staphylococcus aureus Infections in Injection Drug Users: Risk Factors and Prevention Strategies

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Abstract

Infections, in particular soft tissue infections (cellulitis, skin abscesses), are the leading cause for emergency department visits and hospital admissions of drug injection users (IDUs).

Staphylococcus aureus is the most relevant bacterial pathogen in this population. It is the main cause of soft tissue infections and of severe infections such as endocarditis and bacteremia. Moreover, epidemic spread of methicillin-resistant *S. aureus* (MRSA) among IDUs has occurred in Europe and North America. Nasal carriage of *S. aureus* is associated with an increased risk of subsequent *S. aureus* infections, and it has been shown that active IDUs have a higher rate of colonization with *S. aureus* than the general population. However, it is still unknown why an individual carries *S. aureus*. In particular, repeated injections do not appear to be the main predisposing factor for *S. aureus* carriage.

Infections associated with injection drug use are frequently the consequence of the illegal status of street drugs. Harm reduction programs, including needle exchange programs, safer injecting facilities and injection opiate substitution programs can reduce the incidence of infections among severely addicted IDUs.

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Introduction

Injection drug use is associated with several complications (e.g. infectious diseases, drug overdose, violence) that increase morbidity and mortality rates for injection drug users (IDUs) [1–4]. Previous studies have demonstrated that infections are a leading cause of morbidity and hospitalization among IDUs [3]. In a review of autopsies of 274 hospitalized IDUs in California, United States, infections were the most common cause of death [5]. Infections in IDUs are not only a problem for the individual patient, but may affect the community since bloodborne pathogens (e.g. HIV, hepatitis) and resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), may spread

among IDUs and then to non-IDUs. However, complications associated with injection drug use (including many infections) are frequently the consequence of the illegal status of street drugs (contaminated substances, unavailability of sterile injection material, prostitution) rather than of the drug itself [6]. Therefore, opioid substitution programs were developed, with the objective of reducing dependence, morbidity and mortality rates associated with the use of psychoactive substances. In response to the growing problem of the failure of oral substitution treatments to handle addiction in IDUs, injection opiate maintenance programs were started [6–8]. In this review, infections among IDUs, with particular consideration of risk factors and prevention strategies for *S. aureus* infections, will be discussed.

Infections Leading to Hospitalization of IDUs

The epidemiology of severe medical complications among IDUs before injection opiate maintenance programs were available was carefully investigated by *Scheidegger* and *Zimmerli* [2, 3]. They found, in a first retrospective survey of the years 1980 to 1986, that 269 drug-abusing patients (97% were IDUs) had 404 admissions to the Department of Medicine of the University Hospital of Basel, Switzerland. 47% of these patients had at least one infectious complication, and infection was the main cause of hospitalization (31% of admissions), followed by intoxication with oral drugs (28%) and heroin overdose (17%). The most frequent infections were lower respiratory tract infections (24%), viral hepatitis (20%), HIV infection (14%), minor

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genital infection (11%), and thrombophlebitis or soft tissue infection (6%) [3]. The low prevalence of soft tissue infections is explained by the fact that patients admitted to other departments, in particular to the Department of Surgery, were not included in this survey.

In a second retrospective study, charts of 541 IDUs admitted to the same department between 1985 and 1993 were reviewed. An infection was again the main reason for admission among HIV-seropositive IDUs (68% of admissions; incidence density 81.6/1,000 persons-years), and the second most frequent cause of hospitalization among HIV-seronegative IDUs (33%; 11.3/1,000 persons-years), after intoxication (34%) [2].

These data were confirmed by recent studies in other countries. In a prospective cohort study involving 598 IDUs in Vancouver, Canada, between 1996 and 1999, 440 study participants (74%) visited a hospital emergency department at least once, and 210 (35%) were admitted to the hospital at least one time during the study period. The most common reason for an emergency department visit was a soft tissue infection (cellulitis and skin abscess) (17% of visits), and the three most common reasons for hospital admissions were pneumonia (27% of admissions), soft tissue infection (18%), and sepsis (8%). The authors of this study concluded that much of the hospital use was related to complications of injection drug use and may be reduced with the establishment of programs that integrate harm reduction strategies with primary care and addiction treatment [9].

Harm reduction and addiction treatment of severely opioid-dependent drug users are also two of the main goals of the injection opiate substitution programs available in Switzerland, since 1994 [8]. To investigate the impact of such programs on severe infections among participants, a retrospective analysis of hospitalizations due to infection in 175 IDUs for the 3 years before and the period during their participation in an injection opiate maintenance program in Basel, Switzerland was performed (mean duration during program, 2.6 years) [10]. During both periods of the study (i.e. before and during the program) skin infections were the main reason for hospitalization, followed by respiratory tract infections. The injection opiate maintenance treatment did not reduce the incidence or change the spectrum of infections leading to hospitalization among the IDUs studied. However, a majority of these IDUs already routinely used sterile injection material provided by needle exchange programs before entering the injection opiate maintenance program. In addition, other beneficial effects of injection opiate treatment (improvement of health status, reduction of consumption of street drugs, and a decrease in the incidence of HIV) [6–8, 11, 12] are likely to reduce the risk of infection among IDUs in the long term. On the other hand, the fact that the incidence of infection-related hospitalizations during the program did not increase may be interpreted as a stabilization of the health status of the participants.

***S. aureus* Infections in IDUs**

S. aureus is the most relevant bacterial pathogen in IDUs. In particular, *S. aureus* is the most common cause of soft tissue infections (skin abscesses, cellulitis) in this population [13]. Soft tissue infections are, as discussed above, one of the main reasons for emergency department visits and hospitalizations of IDUs [9, 10], but they are also extremely common among IDUs who did not seek medical care. The skin examination of 1,035 IDUs at admission in the Swiss iv heroin substitution programs revealed, for example, an 18% prevalence of abscesses and a 29% prevalence of cellulitis [14]. *S. aureus* is also the main cause of other severe infections in IDUs. It caused, for example, 61% of endocarditis and 57% of bacteremias among IDUs admitted to one hospital in Detroit, Michigan, United States [15, 16], ten of 17 endocarditis episodes (59%) in a cohort of 521 IDUs followed for 5 years in Amsterdam, The Netherlands [17], five of seven cases of sepsis (71%) identified in the study of hospitalized IDUs in Basel, Switzerland, between 1980 and 1986 [3], and it is the most common pathogen causing septic deep vein thrombosis in IDUs [18]. Other infections associated with *S. aureus* in IDUs are septic arthritis, osteomyelitis, and lung abscesses. Furthermore, an association between injection drug use and MRSA [19], and even outbreaks of MRSA infections among IDUs, have been described in the United States [20] and recently in Switzerland [21, 22].

Nosocomial *S. aureus* Infections and IDUs

S. aureus is one of the most important causes of nosocomial infections. In a prevalence survey on nosocomial infections conducted in Swiss intensive care units, *S. aureus* was, overall, the second most frequently isolated microorganism (13%), after Enterobacteriaceae (28%), and the main cause for bloodstream (17%) and surgical site infection (15%) [23].

Nosocomial bloodstream infections require special consideration, since they are frequent (e.g. 12% of all nosocomial infections reported in a study on more than 10,000 European intensive care patients) [24], and are associated with significant attributable mortality (4 to 30%) and costs (USD 4,000 to USD 40,000) [25]. More than 85% of primary nosocomial bacteremias are intravascular catheter-related [25] and it has been shown that the mortality rate attributed to catheter-related *S. aureus* bacteremia (8.2%) significantly exceeds the rates for other pathogens [26]. These aspects are particularly relevant to hospitalized IDUs, because most of them need a vascular access, frequently a central venous catheter, since peripheral line insertion and even blood drawings are often difficult or impossible in IDUs. Several IDUs use the central venous catheter during hospitalization to inject street drugs, which are often contaminated, thus further increasing the risk of catheter infection, which is already higher in this population because of the higher *S. aureus* colonization rate, of preexistent pathologies of the veins (thrombophlebitis,

etc.), of the difficult line insertion, and of the frequent use of central venous catheters for drawing of blood samples from these patients [27]. A recent prospective study analyzing 1,379 hospital admissions in Italy confirmed that, at least in HIV-infected patients, active injection drug use is independently associated with nosocomial bloodstream infections [27]. The most common pathogen associated with bacteremia in this study was *S. aureus* (29.8% of all nosocomial bloodstream infections and 32.3% of all catheter-related bloodstream infections).

Thus, strategies focusing on the prevention of catheter-related bloodstream infections (CRBSI) are particularly important for hospitalized IDUs. Several preventive measures regarding skin disinfection, sterile insertion, dressing, handling and replacement of the catheter have been shown to reduce the incidence of CRBSI and have been recommended [25, 28]. As a result of the implementation of these measures, during the last 10 years the incidence of intravascular device-associated bloodstream infections has decreased in the United States by nearly 40% [29]. Educational programs also proved to be very effective in reducing rates of CRBSI [30, 31]. An additional option for the prevention of CRBSI is the use of anti-infective catheters [32–34].

Risk Factors for *S. aureus* Infection in IDUs Nasal *S. aureus* colonization

It has previously been shown that active IDUs have a higher rate of colonization with *S. aureus* (on the skin and nasal) than the general population [35]. This may explain the high incidence of *S. aureus* infections among IDUs, since the colonized nose provides a reservoir from which the skin is seeded [36], and since nasal carriage is associated with an increased risk of subsequent *S. aureus* infections [37, 38]. The hypothesis that most *S. aureus* infections in IDUs originate from *S. aureus* colonizing the nose is also supported by the findings of two studies investigating the source of *S. aureus* in infected patients. In the first study, Tuazon and Sheagran [39] studied ten IDUs with *S. aureus* endocarditis. All were *S. aureus* carriers, and in each case, the phage type of the carried organism matched that of the organism recovered from the blood. In the second study, genotypically identical strains of *S. aureus* were simultaneously isolated from nasal and wound cultures in 43 (81%) of 53 patients with soft tissue infections who had *S. aureus* with concordant antimicrobial sensitivity patterns in both nasal and wound sites [40].

It is, however, still unknown why an individual carries *S. aureus*. A number of host characteristics have been proposed as risk factors for *S. aureus* carriage. Examples include anatomic abnormalities of the nose, certain leukocyte antigens, immunological status, viral infections of the upper respiratory tract, age, ethnicity, hospitalization [37], hormonal status in women [41], previous use of antibiotics [41], use of nasal steroid sprays [42], and the presence of atopic dermatitis [43].

Based on the observation of higher *S. aureus* carriage rates among patients with insulin-dependent diabetes mellitus, patients on hemodialysis or continuous ambulatory peritoneal dialysis and in iv drug addicts, repeated puncture of the skin by needles has been proposed as a risk factor for nasal *S. aureus* carriage [37, 44, 45]. It was thought this association was further supported by a report showing an increase in the *S. aureus* carriage rate in patients starting allergen-injection immunotherapy, suggesting the repeated injection increased the risk of colonization with *S. aureus* in this population [45]. In a newer study of 45 outpatients (non-IDUs) undergoing desensitization therapy with allergen injection and 84 healthy controls, the nasal *S. aureus* carriage rate among patients was also higher than in controls (46.7% vs 26.2%; $p = 0.019$). However, the only independent predictor of nasal *S. aureus* carriage in this study was the presence of atopic dermatitis or eczema (OR 4.4; 95% CI 1.2–16.0; $p = 0.02$). The probability of nasal *S. aureus* carriage was 88.9% for patients receiving allergen injections and having atopic dermatitis or eczema, and 36.1% for patients receiving allergen injections without atopic dermatitis or eczema [46]. Thus, factors other than the regular use of needles, particularly abnormalities related to the atopic constitution of these patients, may predispose this population for *S. aureus* carriage.

The results of two other studies on IDUs support the hypothesis that regular injections per se are not the main predisposing factor for *S. aureus* carriage. In the first study, 94 IDUs treated in an injection opiate maintenance program (injecting non-contaminated heroin with sterile equipment at least twice daily) had a significantly lower nasal *S. aureus* carriage rate (22%) and overall colonization rate (i.e., *S. aureus* carriage in the nose and/or pharynx and/or the skin) (39%) than 70 IDUs participating in a conventional oral methadone program (respectively 43% and 60%; $p = 0.005$ and $p = 0.009$). In a multivariate model, being in the oral methadone program was the only significant risk factor for *S. aureus* carriage (OR 2.27; 95% CI 1.19–4.31; $p = 0.012$). It is important to note that 66% of the patients in the oral methadone program continued to use iv street drugs [47]. In the second study of 217 active and former drug users, no association between iv drug use and nasal colonization by *S. aureus* was found, while nasal *S. aureus* carriage was independently correlated with inhalational drug use in HIV-infected persons [48]. These findings suggest that injection of contaminated drugs and inhalational drug use may promote nasal *S. aureus* colonization, probably by damaging the nasal mucosa, since damaged nasal mucosa is more likely to become colonized by *S. aureus* [49].

Contaminated Drugs and Drug-Use Paraphernalia

Organisms causing infections in IDUs may come from contaminated needles or saliva, when the needle is licked before injection, or the injection site is “cleaned” with saliva. This mechanism of infection has been associated for ex-

ample with cases of endocarditis or osteomyelitis caused by *Eikenella corrodens* [50, 51]. Lemon juice used in heroin abuse has been implicated as a source of *Candida albicans* in outbreaks of systemic candidiasis in IDUs [52]. Epidemics of *Pseudomonas aeruginosa* endocarditis have been described in IDUs, mainly abusers of pentazocine and tripeleminamine, and are presumably associated with the mixing of drugs in contaminated water [53]. Finally, a recent outbreak of a clonal strain of group A streptococcus among drug users in Bern, Switzerland, may have been caused by contaminated cocaine or its containers [54], and an epidemic of wound botulism in California, may have resulted from contamination of black tar heroin most likely when it was diluted ("cut"), possibly with soil [55]. Inhalation drug-use paraphernalia were identified as potential vehicles of transmission of *S. aureus* in inhalation drug users [56]. However, contaminated drugs or paraphernalia have probably only a minor role in the transmission of *S. aureus*. Tuazon et al. [57] did not find *S. aureus* contamination of either street heroin or injection paraphernalia, and showed that most samples of street heroin had antibacterial effects against *S. aureus* and *Bacillus cereus*, possibly because of the quinine content of the drug mixture [58]. Also in a recent study, only one of 58 heroin samples examined in the United Kingdom yielded *S. aureus* [59].

Drug Use Environment

It has previously been shown that close personal contact may facilitate outbreaks of *S. aureus* skin infections, in particular if involved individuals frequently present minor skin wounds. Such epidemics were described, for example, among members of football and wrestling teams [60,61], or among river rafting guides who shared communal housing [62]. Similarly, *S. aureus* may spread among drug users in shooting galleries, crack houses or other sites where drugs are consumed, and where hygiene is usually poor. Indeed, Craven et al. [63] reported an MRSA outbreak among IDUs who frequented the same shooting gallery, and frequent and close social contacts was considered to be the most likely explanation for the epidemic spread of a single clone of MRSA among IDUs in Zurich, Switzerland [21].

General Risk Factors for Infections in IDUs

In addition to risk factors that specifically increase the risk of *S. aureus* infections, other characteristics or habits of IDUs are associated with bacterial infections in general. Subcutaneous or intramuscular injection of drugs ("skin-popping"), injection of a cocaine and heroin mixture ("speedball"), use of a dirty needle, higher frequency of injection, and drawing blood into the syringe before injection of drugs ("booting") (in particular in individuals who do not engage in skin-popping) have been identified as risk factors for soft-tissue abscesses [17, 64]. Women are at greater risk for skin abscesses, presumably because female IDUs have fewer visible veins than men do and may have greater difficulty in accessing their veins [17]. Infection with

HIV was associated with soft-tissue abscesses in some, but not in all studies [17, 64]. Finally, endocarditis in IDUs was associated with HIV infection, previous history of endocarditis [17], and cocaine use [65]. It is unknown whether the increased risk related to cocaine is caused by systemic or immunosuppressive effects of cocaine or by injection habits (more frequent injections).

Prevention of *S. aureus* Infections in IDUs

The most effective means of preventing infections among IDUs is, obviously, treatment of drug abuse, with consequent reduction or termination of injection drug use. Improving the quality of treatment services by adding counseling, medical care, and psychosocial services to a methadone therapy, for example, can significantly reduce drug use [66]. Further preventive strategies are directed toward risk factors identified for infections in IDUs. Simple skin cleaning before injection decreases the risk of soft-tissue abscesses and endocarditis [64, 67]. Needle exchange programs reduce the use of dirty needles and the incidence of abscesses [68], and may be even more effective if combined with primary health care delivery systems [69], with a soft tissue infection clinic [70], or with safer injecting facilities where IDUs can also inject pre-obtained illicit drugs [71]. Finally, injection opiate substitution programs for severely addicted IDUs improve health status and social functioning, reduce the self-reported use of illicit drugs and criminal activity [6–8, 11], may decrease the incidence of HIV and hepatitis A [12], and reduce the prevalence of skin abscesses and cellulitis [14].

In conclusion, IDUs are at high risk for both community-acquired and nosocomial infections. The main bacterial pathogen causing these infections is *S. aureus*. The high incidence of *S. aureus* infections among IDUs can be explained, at least in part, by the high *S. aureus* colonization rate in this population, which predisposes for subsequent infections with this organism. *S. aureus* is not only a threat because of the relevant morbidity and costs associated with *S. aureus* infections, but also because of the spread of antibiotic-resistant strains, particularly of MRSA. Continuous surveillance of the epidemiologic situation is necessary to rapidly identify the beginning of MRSA outbreaks among IDUs.

The understanding of the mechanisms leading to *S. aureus* colonization would allow implementation of efficacious prevention strategies for IDUs, but also for other patients at risk for *S. aureus* colonization and infection (e.g. insulin-dependent diabetics, hemodialysis patients). However, these mechanisms are still unknown. In particular, repeated injections do not appear to be the main cause of increased *S. aureus* carriage, and further studies are needed to investigate this question.

Infections associated with iv drug use are frequently the consequence of the illegal status of street drugs. Harm reduction programs including needle exchange programs, safer injecting facilities and injection opiate substitution

programs can reduce the incidence of infections among severely addicted IDUs.

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