Review

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Shooting up: the interface of microbial infections and drug abuse

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Illicit drug control has been on the global agenda for more than a century. Infections have long been recognized as one of the most serious complications of drug abuse. Drug users are susceptible to pulmonary, endovascular, skin and soft tissue, bone and joint, and sexually transmitted infections caused by a wide range of bacterial, viral, fungal and protozoal pathogens. In addition, injection drug users are at increased risk for parenterally acquired infections such as human immunodeficiency virus, hepatitis B virus, hepatitis C virus, tetanus and malaria. Factors related to drug use, such as unsterile injection practices, contaminated drug paraphernalia and drug adulterants, increase the exposure to microbial pathogens. Illicit drugs also affect several components of the complex immune system and thus modulate host immunity. In addition, lifestyle practices such as multiple sexual partners, overcrowded housing arrangements and malnutrition serve as co-factors in increasing the risk of infection. In this review we present an overview of the unique aspects of microbial pathogenesis, immune modulation and common infections associated with drug use. We have restricted the definition of drug abuse to the use of illegal drugs (such as opiates, marijuana, cocaine, heroin and amphetamines), not including alcohol and nicotine.

Introduction

Illicit drug control has been on the global agenda for more than a century. The year 2009 marked the end of the first century of drug control, which began at the Shanghai Opium Commission in 1909 (Lowes, 1966). The United Nations Office on Drugs and Crime (UNODC) estimates that in the year 2007, 172 to 250 million people worldwide (~ 5%) used illicit drugs at least once (UNODC, 2009). There are an estimated 11 to 21 million injection drug users (IDUs) globally, with over 10 million of them (~70%) living in developing and transitional countries (Aceijas *et al.*, 2004). Infections have long been recognized as one of the most serious complications of drug abuse (Hussey & Katz, 1950; Scheidegger & Zimmerli, 1989). Drug users are susceptible to pulmonary, endovascular, skin and soft tissue, bone and joint, and sexually transmitted infections caused by a wide range of bacterial, viral, fungal and protozoal pathogens (Levine & Brown, 2005). In addition, IDUs are at increased risk for parenterally acquired infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), tetanus and malaria. Factors related to drug use, such as unsterile injection practices, contaminated drug paraphernalia and drug adulterants, increase exposure to microbial pathogens (Gordon & Lowy, 2005). Illicit drugs also affect several components of the complex immune system and thus modulate host immunity

(Friedman *et al.*, 2006). In addition, lifestyle practices such as multiple sexual partners, overcrowded housing arrangements and malnutrition serve as co-factors in increasing the risk of infection. In this review we present an overview of the unique aspects of microbial pathogenesis, immune modulation and common infections associated with drug use. We have restricted the definition of drug abuse to the use of illegal drugs (such as opiates, marijuana, cocaine, heroin and amphetamines), not including alcohol and nicotine.

Pathogenesis of microbial infections in drug users

Infections in drug users may be acquired from contaminated drugs, drug paraphernalia, unique drug preparation practices or from the user's commensal flora.

Drug contaminants and adulterants

Black tar heroin is a crude and unpurified derivative of opium that originated in Mexico (Bucardo *et al.*, 2005). The drug is often diluted ('cut') at several points along the distribution line with methamphetamines, starch, lidocaine and even shoe-polish-impregnated paper. During this process, bacterial spores can be introduced into the final product. Clostridial spores are heat resistant (surviving

temperatures up to 72 °C) and when introduced into black tar heroin easily survive the brief heating period most drug users employ (Bleck, 2005). The focus of insoluble material, haemorrhage and devitalized tissue at the injection site provides an ideal anaerobic microenvironment. Clostridial infections, such as wound botulism, tetanus and necrotizing fasciitis, have been reported among black tar heroin users (Passaro *et al.*, 1998; Pascual *et al.*, 2003; Dunbar & Harruff, 2007). Heroin contamination by other spore-forming bacteria such as *Bacillus* spp. is also documented (McLauchlin *et al.*, 2002). In a case of *Bacillus cereus* cellulitis in an IDU, the isolate recovered from the soft tissue specimen was identical to that obtained from the sample of used heroin, pointing to the drug as the likely source of infection (Dancer *et al.*, 2002). In the UK and Germany, 11 deaths caused by drug-related anthrax were reported in IDUs using contaminated heroin (Christie, 2010). The same strain of *Bacillus anthracis* was recovered from both countries, suggesting the possibility of a common source of drug supply and contamination prior to distribution.

Additives introduced into the drug to enhance its effects or attenuate its side effects may lead to unusual complications. The immunomodulatory drug levamisole was added to cocaine supplies in North America and Europe to potentiate the euphoric effects (Zhu *et al.*, 2009; Fucci, 2007). Drug users presented with febrile agranulocytosis leading to a variety of infectious complications. Levamisole is known to cause reversible neutropenia and was implicated as the likely cause (Drew *et al.*, 1980).

Adulterants (or cutting agents) may be deliberately added to drugs to 'extend' their effects, resulting in lower purity, lower cost and increased profit. Drug users in Tijuana, Mexico, were reported to use methamphetamines of various colours such as clear (ice), white, yellow and pink, serving as proxy indicators for purity (Strathdee *et al.*, 2008a). IDUs using coloured methamphetamines were more likely to develop cutaneous abscesses (34 %) as compared to those injecting the clear variety (24 %). Poor drug purity may be related to development of abscesses though further study is needed to understand the mechanism of this association.

Drug paraphernalia and drug use environment

Disposable needles, syringes, metal needles wedged onto droppers, rolled paper, improvised filters (cotton), 'cooking' equipment (spoon or bottle cap used to heat the drug to achieve solubility) constitute the 'works' or paraphernalia commonly used to inhale or inject drugs.

The first community outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in the USA was reported among drug users in Detroit (Levine *et al.*, 1986). Person-to-person spread via contaminated needles was the suspected mode of transmission. Transmission of *S. aureus* has also been linked to inhalational drug paraphernalia

(straws, matchbooks), which may be related to the high density of staphylococci in the nares of carriers and the ability of the organisms to survive for prolonged periods on environmental surfaces (Quagliarello *et al.*, 2002). Craven *et al.* (1986) reported a clonal MRSA outbreak among IDUs that was linked to a 'shooting gallery' (a common place used by drug users to inject drugs and share equipment). Drug users can also transmit *S. aureus* via close physical contact (Murphy *et al.*, 2001), which was implicated in the epidemic spread of MRSA among IDUs in Zurich (Fleisch *et al.*, 2001).

Transmission of blood-borne viral pathogens such as HIV, HBV, HCV and human T cell lymphotropic virus (HTLV) through needle sharing practices among IDUs has been widely documented (Strathdee & Stockman, 2010; van Houdt *et al.*, 2009; Hagan *et al.*, 2010; Blomberg *et al.*, 1994). However, the possibility of viral transmission following the use of shared drug preparation equipment in the absence of injection is also a concern (Quellet & Bailey, 2003). An examination of paraphernalia from a Miami shooting gallery detected HIV-1 DNA in cotton filters, cookers and water used to dissolve drugs (Shah *et al.*, 1996). Although the presence of HIV-1 DNA does not distinguish between infectious and non-infectious virus, it does suggest a risk of infection from the reuse of such contaminated equipment. In addition, given the strong and compelling evidence of blood-borne virus transmission via shared drug paraphernalia, we do not need to rely on DNA evidence alone.

An outbreak of malaria induced by *Plasmodium vivax* was reported in a cluster of heroin users in Spain. The patients gave no history of travel to endemic areas but did report the sharing of injection equipment. The source of infection was traced to a drug user with a history of travel to the Republic of Equatorial Guinea (Gonzalez Garcia *et al.*, 1986). A report of transmission of *Borrelia recurrentis* via contaminated needles among IDUs suffering from tick-borne relapsing fever underlines the possibility of the survival and spread of a wide range of pathogens through drug paraphernalia (López-Cortés *et al.*, 1989).

'Cotton fever' syndrome, characterized by acute-onset fever and myalgia is a benign, self-limiting condition seen in intravenous narcotic addicts (Shragg, 1978). Though the exact causative mechanism is unknown, symptoms are seen to follow the injection of heroin reclaimed from previously used cotton filters (Harrison & Walls, 1990). The endotoxin released by *Enterobacter agglomerans*, which colonizes cotton plants, is believed to play a role (Ferguson *et al.*, 1993).

Drug preparation practices

A series of groin abscesses caused by '*Streptococcus milleri*' was reported among drug users in Scotland, where tablets of buprenorphine and temazepam were crushed between the teeth prior to dissolution, and injected into skin

cleaned with saliva (Hemingway *et al.*, 1992). An intravenous combination of pentazocine and blue-coloured antihistamine tripeleminamine, referred to as tabs or T's and blues, was popular in Chicago in the late 1970s. It was associated with an outbreak of infective endocarditis caused by *Pseudomonas aeruginosa* when the tablets were dissolved in contaminated tap water before injection (Levin *et al.*, 1984). Drugs are often dissolved in mild acids, such as tartaric or citric acid, to enhance the breakdown of tissues at the injection site, which also serve as a good culture medium. Preserved lemon juice used to dissolve heroin or cocaine prior to injection was identified as a source of endogenous *Candida albicans* endophthalmitis in drug users (Shankland & Richardson, 1989; Albin *et al.*, 2007). *Paenibacillus larvae* bacteraemia was reported from a group of IDUs who self-injected honey-prepared methadone containing *Paenibacillus larvae* spores (Rieg *et al.*, 2010). *Paenibacillus larvae* is the causative agent of American foulbrood in honey bees and its highly resistant spores can survive in honey for several years (Hasemann, 1961).

Role of commensal flora

The drug user's commensal flora serves as a reservoir of a wide range of potential pathogens. The majority of such infections are caused by *S. aureus* or streptococci followed by anaerobic cocci and aerobic Gram-negative rods (Gordon & Lowy, 2005). IDUs have a higher rate of nasal and skin carriage of *S. aureus* (including MRSA), associated with an increased risk of subsequent staphylococcal infections (Al-Rawahi *et al.*, 2008; Huang *et al.*, 2008; Kluytmans *et al.*, 1997). A new clonal type, USA-300, accounts for the majority of MRSA isolates, supplanting the previous 100% prevalence of USA-500 in the IDU population (Al-Rawahi *et al.*, 2008). While the exact cause is unknown, repeated damage to the nasal epithelium by drug inhalation or skin damage by drug injection might play a role (Kluytmans *et al.*, 1997; Kirmani *et al.*, 1980). Cohen *et al.* (2007) have identified a novel association between MRSA skin infections and methamphetamine use. Methamphetamine use causes formication, a sensation of 'something crawling underneath the skin', which leads to skin-picking behaviour, local breaches in the cutaneous barrier and portals of infection.

Practices such as needle or skin licking prior to 'shooting up' may lead to contamination with organisms from the oral flora. *Eikenella corrodens* is a fastidious, Gram-negative bacillus found as part of the endogenous flora of the oral cavity. Moistening of injection equipment with saliva favours the introduction of the bacilli into the injection site (Deutscher & Perlman, 2008). The presence of devitalized tissues favours the survival of *E. corrodens*, and infections such as endocarditis, meningitis, osteomyelitis, cellulitis and skin abscesses have been reported (Olopoenia *et al.*, 1994; Swisher *et al.*, 1994). *E. corrodens* infections have also been reported in methylphenidate drug users who crush tablets with their teeth prior to injection (Silpa &

D'Angelo, 1980). Endogenous fungal endophthalmitis caused by orally derived *Candida* spp. has been reported with the use of buprenorphine. Diversion of the sublingual drug from the oral cavity after it was dispensed followed by intravenous injection was implicated (Aboltins *et al.*, 2005).

Drugs of abuse and immune modulation

The recreational use of illicit drugs has aroused concerns that drug abuse-mediated immune dysfunction increases host susceptibility to microbial pathogens and this has assumed greater importance with the onset of the AIDS pandemic (Friedman, 1996; Siegel, 1986). Drugs of abuse affect several components of the complex immune system, either enhancing or suppressing the function of immune response cells and factors, such as chemokines and cytokines, produced by them (Friedman *et al.*, 2006). Effects on the immune system may be mediated directly through activation of cognate receptors on immune cells or indirectly through drug interactions in the central nervous system (CNS) as shown in Table 1. Certain common mechanisms involved in drug-induced immunomodulatory effects are Th1 (cellular)/Th2 (antibody-mediated) responses leading to inhibition of Th1-associated [interleukin (IL-)12, gamma interferon (IFN- γ)] or elevation of Th2-associated (IL-4) cytokines (Bussiere *et al.*, 1992; Pacifici *et al.*, 2003; Cabral & Staab, 2005).

Direct immunomodulatory effects

Cannabis sativa or marijuana has been shown to exert immunomodulatory effects by binding to the two major cannabinoid receptors CB1 (brain and certain peripheral tissues) and CB2 (immune cells) (Klein *et al.*, 2003). Binding to these receptors is associated with a decrease in lymphocyte proliferation, antibody formation, cytotoxic activity and cytokines/chemokine production (Friedman *et al.*, 2006).

Opiates also affect the immune system directly through opioid receptors on immune cells leading to reduced phagocytosis and chemotaxis (McCarthy *et al.*, 2001). Methadone, used for the treatment of opioid dependence, has been shown to enhance HIV replication in infected cells. The upregulation of CCR5 receptor expression and downregulation of β -chemokine production may account for the M-tropic infection of macrophages following the effect of methadone (Li *et al.*, 2002).

Indirect immunomodulatory effects

Psychoactive drugs such as opium, morphine and heroin also exert immunomodulatory effects via indirect mechanisms. Opiate receptors have been identified in the nervous system, with the classical receptor subtypes mu, kappa (κ) and gamma (γ) shown to predominate. Opiates directly ligate mu and γ receptors leading to receptor-mediated suppression of macrophage phagocytosis, chemotaxis and cytokine production (Chao *et al.*, 1990). Opiates also

Table 1. Effects of common drugs of abuse on immune function and susceptibility to microbial pathogens

Drug of abuse	Mechanism of immune modulation	Effect on immune system	Susceptibility to pathogens	Reference
Opioids (opium, morphine, heroin)	Direct – via opioid receptors (immune cells) Indirect – via opioid receptors (CNS), hypothalamic pituitary axis	↓ Phagocytosis ↓ Antibody formation ↓ Mitogen proliferation ↓ ↑ Cytokine formation ↓ NK cell activity ↓ Chemotaxis	<i>Salmonella typhimurium</i> , <i>Toxoplasma gondii</i> , HSV-1, <i>Candida albicans</i>	MacFarlane <i>et al.</i> (2000), Chao <i>et al.</i> (1990), Panasiak <i>et al.</i> (1990), Tubaro <i>et al.</i> (1983)
Cannabinoids (marijuana)	Direct – via cannabinoid receptors CB1 (brain and peripheral tissue) Indirect – CB2 (immune cells)	↓ Cytokine formation ↓ Lymphocyte proliferation ↓ NK cell activity ↓ Neutrophil function ↓ Antibody formation	HSV, <i>Listeria monocytogenes</i> , <i>Legionella</i> spp., staphylococci, <i>Treponema pallidum</i> , HIV, <i>Naegleria fowleri</i> , <i>Acanthamoeba</i> spp.	Mishkin & Cabral (1985), Morahan <i>et al.</i> (1979), Newton <i>et al.</i> (1994), Huber <i>et al.</i> (1980), Paradise & Friedman (1993), Sidney <i>et al.</i> (1997), Burnette-Curley <i>et al.</i> (1993), Cabral & Marciano-Cabral (2004)
Cocaine (crystal form – crack)	Indirect – via σ -1 receptor expressed in the central and peripheral nervous system	↓ ↑ Cytokine formation ↓ Lymphocyte proliferation ↓ NK cell activity ↓ Antibody formation ↓ Cellular hypersensitivity	HIV progression (↑ viral load, ↓ CD4 ⁺ :CD8 ⁺ ratio) LP-BM5 retrovirus	Roth <i>et al.</i> (2002), Darban <i>et al.</i> (1993)
Amphetamines (ecstasy/speed)	Indirect – via dopamine release from CNS	↓ Cytokine formation (IL-2) ↓ Cytotoxic T lymphocyte production	HIV, HCV	Phillips <i>et al.</i> (2000), Käll & Olin (1990)

NK, Natural killer.

interact with neural cells via the hypothalamic pituitary axis by stimulating the release of corticotrophin-releasing hormone and adrenocorticotrophic hormone. This results in an increase in serum levels of glucocorticoids and suppression of several immune parameters (Friedman *et al.*, 2006). Increased production of immunosuppressive cytokines such as TGF- β is another indirect method by which opiates suppress immunity (Peng *et al.*, 2001).

Cocaine mediates indirect effects on the immune system through the sigma-1 (σ -1) receptor located in the brain and peripheral nervous system (Friedman *et al.*, 2003). In the pathogenesis of HIV, cocaine has been shown to increase viral replication in peripheral blood mononuclear cells, increase viral load and decrease the CD4⁺:CD8⁺ ratio (Matsumoto *et al.*, 2002). Notwithstanding experimental limitations and challenges in extrapolation of *in vitro* data, evidence suggests that illicit drugs act, at least, as cofactors that can increase the severity of microbial infections by altering host resistance.

Microbial pathogens and their association with drug use

Bacterial infections

***S. aureus*.** *S. aureus* is the most common pathogen causing skin and soft tissue infections in IDUs with community-associated MRSA accounting for a high proportion (Lowy

& Miller, 2002; Lloyd-Smith *et al.*, 2010). Infections are usually minor in nature; however, severe forms such as osteomyelitis, bacteraemia, septic deep vein thrombosis and endocarditis are not uncommon (Cooke *et al.*, 2010; Föh *et al.*, 2002).

Genetic analysis of strains from drug users in the UK demonstrated the polyclonal nature of *S. aureus* in the lesions of the IDUs with marked variability in toxin gene content (Monk *et al.*, 2004). The relatively high frequency of the sequence type (ST) 59 genotype suggests that it could be a common clone among IDUs in the region. In a more recent study from Brighton, UK, this ST59 clone appears to have disappeared from the local IDU population to be replaced by the single MRSA clone ST1 (Atkinson *et al.*, 2009). This shift in the population structure of MRSA in IDUs from epidemic hospital-acquired clones to single MRSA clones suggests that IDUs form a unique group for *S. aureus* transmission.

Investigation of an outbreak in Alberta, Canada, identified the USA 300 strain of community-associated MRSA to be increasingly linked with infections in drug users and homeless populations (Gilbert *et al.*, 2006). The strain possessed the staphylococcal cassette chromosome *mec* type-IV genetic element, which contains the *mecA* resistance gene, the PVL determinant and the *spa* type 008. The majority of the infections in the outbreak were

community acquired and severe in nature, with a high proportion requiring intravenous antimicrobial therapy.

Nosocomial infections caused by *S. aureus* are particularly relevant to hospitalized IDUs since many of them need central vascular access (Petrosillo *et al.*, 2002). IDUs may also use the central access to inject illicit drugs; thus, furthering the risk of catheter infection (Bassetti & Battagay, 2004).

Group A streptococci (GAS). IDUs represent an increasing proportion of patients with invasive group A streptococcal disease (Léchoy *et al.*, 2001; Lamagni *et al.*, 2008). In 2000, the UK witnessed a sudden increase in GAS infections in IDUs, sparking off a nationwide investigation (Efstratiou *et al.*, 2003). Cases were reported throughout England and Wales, and the majority of them presented with skin sepsis and bacteraemia. A total of 12 different M serotypes were detected, which included M1, M4, M11 and M22, predominating early in the outbreak, and the 'higher types', M78, M82, M83, M87 and M89, emerging during the later years. Based on *emm* typing, GAS strains from IDUs in the UK were found to be predominantly *emm*82 and *emm*83 types, which were uncommon in the non-IDU population, and furthermore, *emm*82 strains also appear to be clonal (Curtis *et al.*, 2007). An outbreak of soft tissue infections among cocaine users in Switzerland caused by the clonal GAS strain M type 25 was reported and the majority of the infected drug users obtained their drugs from a common source (Böhlen *et al.*, 2000). Drug dealers often hide cocaine in their mouths to avoid the attention of the police. GAS may have spread to drug users by contamination of the plastic bags containing the cocaine or via respiratory droplets from a colonized drug dealer. Thus, GAS invasive soft-tissue infections may present in an epidemic fashion among IDUs even in the absence of shared paraphernalia.

***P. aeruginosa*.** Outbreaks of endocarditis caused by *P. aeruginosa* serotype 011 were reported from Chicago in the 1980s in drug users injecting the pentazocine–tripeleppamine combination (Shekar *et al.*, 1985). Contamination of drug paraphernalia during elaborate drug preparation techniques prior to self-injection is likely to have initiated the outbreak. In one method of drug preparation, drug tablets were placed in a match book, crushed by chewing, suspended in tap water or toilet water in a small unsterile container, filtered through a piece of cotton or a cigarette filter and injected using shared syringes. In addition, pentazocine–tripeleppamine is usually not boiled prior to use (in contrast to heroin), leading perhaps to a greater chance of survival for the contaminating bacteria. Botsford *et al.* (1985) studied microbiological growth in pentazocine–tripeleppamine and found that *P. aeruginosa* strains survived in the drug combination as opposed to the complete inhibition of strains of *S. aureus* (used as controls). A resurgence of *P. aeruginosa* endocarditis in IDUs, was noted in

Detroit between 2006 and 2008 and though pentazocine–tripeleppamine were no longer available in the streets, drug users did admit to using syringes cleaned with unboiled tap water (Reyes *et al.*, 2009). *P. aeruginosa* has also been associated with other infections in IDUs including septic arthritis (typically affecting the sternoclavicular joint) (Brancós *et al.*, 1991), spinal and disc space infections (Chuo *et al.*, 2007; Kaplan, 1974) and osteomyelitis (Boll & Jurik, 1990).

Spore-forming bacterial infections

Tetanus. Tetanus in IDUs appears to be the case of a re-emergence of an old disease in a new setting. First described in subcutaneous morphine users, tetanus is arguably the oldest infection associated with the IDU (Anon, 1876; Levinson *et al.*, 1955). Subcutaneous or intramuscular injection ('skin popping') of contaminated heroin is the most common implicated factor (Bartlett, 1991). Though limited data are available on anti-tetanus antibody levels in IDUs, a study from Guipuzcoa, Spain (Gilla *et al.*, 1994), showed that more than half of the subjects lacked protective antibodies (50.8%) – indicating the existence of a large pool of unprotected and highly susceptible drug users.

Tetanus outbreaks among IDUs have been reported worldwide and are often associated with poor outcome and high mortality (Beeching & Crowcroft, 2005; Hahné *et al.*, 2006; Pascual *et al.*, 2003). An increase in the incidence of tetanus among IDUs may be attributed to an alteration in the adulterants or bacteriological profile of circulating street heroin. The powdered form of heroin is poorly soluble in water and is often dissolved in mild acids followed by heating in a spoon prior to use. The mild acid (pH ~2.5) kills the non-spore-bearing bacteria, which serve as a source of competition to the surviving spore-bearers and the heat treatment stimulates the spores to germinate (Brazier *et al.*, 2003). Simultaneous injection of heroin and cocaine ('speed balls') may induce soft tissue ischaemia making conditions favourable for anaerobic growth (Murphy *et al.*, 2001). To improve laboratory detection, Akbulut *et al.* (2005) developed an efficient real-time PCR assay to amplify the *C. tetani* neurotoxin (TeNT) gene in wound specimens from IDUs.

Other clostridial infections. Outbreaks of wound botulism among IDUs have increased in conjunction with the use of black tar heroin (Passaro *et al.*, 1998; Brett *et al.*, 2004; Kalka-Moll *et al.*, 2007; Werner *et al.*, 2000; Barry *et al.*, 2009). Though most commonly associated with heroin use, botulism has also been reported following intranasal cocaine abuse (Kudrow *et al.*, 1988). An unprecedented outbreak of severe soft tissue infection among heroin IDUs was reported from Glasgow, Scotland (CDC, 2000). The most frequently isolated pathogen was *Clostridium novyi* type A and findings pointed to contaminated heroin as the source of infection. The occurrence of similar

contemporaneous outbreaks in Ireland and England reflected specific recognized routes of heroin distribution along which the infection had been spread (Jones *et al.*, 2002; McGuigan *et al.*, 2002). Other pathogenic clostridia such as *Clostridium histolyticum*, *Clostridium sordellii*, *Clostridium perfringens*, *Clostridium septicum* and *Clostridium bifermentans* have also been reported following 'muscle popping' in IDUs (Brazier *et al.*, 2002).

In the setting of IDUs, diagnostic microbiology departments should be alert to the possibility of isolating unusual clostridia. The origins of street heroin in most parts of the world are found in South-West Asia, particularly Afghanistan. Given the turmoil in the region and non-sterile methods of production and transport, contamination is possible at virtually any stage in the process.

Anthrax. Since December 2009, 31 cases of anthrax, including 11 deaths, have been confirmed among drug users in Scotland (Booth *et al.*, 2010; Ramsay *et al.*, 2010). Contamination of heroin or a cutting agent along the supply chain is considered to be the vehicle of infection. Patients presented with a new pattern of infection, previously described as injectional anthrax, characterized by inflammation and abscesses at sites of heroin injection (Ringertz *et al.*, 2000; Lalitha *et al.*, 1988). A fatal case of anthrax also occurred in a heroin user in Germany in December 2009 (Radun *et al.*, 2010). It is unclear whether there is a link between this case and the anthrax outbreak among IDUs in Scotland. If the hypothesis of a potential link to the Scottish cases proves true, it might well be that several countries worldwide have been supplied with the same contaminated batch of heroin.

Tuberculosis. Drug use has been associated with a higher prevalence of latent and active tuberculosis and HIV-infected drug users are at particularly high risk (Reichman *et al.*, 1979; Perlman *et al.*, 1995; Markowitz *et al.*, 1993; Friedman *et al.*, 1996; Oeltmann *et al.*, 2009). A cluster of tuberculosis cases was identified in Seattle, USA, among East-African immigrants with a history of illicit marijuana use (Oeltmann *et al.*, 2006). Isolates shared identical genotyping patterns, which in the state of Washington was exclusive to this outbreak. Patients reported frequent 'hotboxing', the practice of group smoking of marijuana in a vehicle with the windows closed so that exhaled smoke is repeatedly inhaled. Indigenous practices such as the sharing of a marijuana water pipe ('bong') in Australia and using a common 'chilam' or earthen tubular pot filled with tobacco and burning coal among opium users in India have been reported to favour tuberculosis transmission (Munckhof *et al.*, 2003; Mathur & Chaudhary, 1996). 'Shotgunning' or inhaling smoke from illicit drugs and exhaling it directly into another's mouth has been associated with *M. tuberculosis* transmission among a group of exotic dancers and their contacts (McElroy *et al.*, 2003).

In March 1992, a cluster of tuberculosis cases among drug users was identified in San Mateo County, California

(Leonhardt *et al.*, 1994). All patients gave a history of cocaine abuse that included visiting one of the two crack houses of the neighbourhood. The index case contributed to the transmission as a transient resident of several dwellings. Crack use has been associated with impairment of pulmonary function and exacerbation of coughing, which could facilitate tuberculosis transmission (CDC, 1991). Because of delays in diagnosis and treatment, cocaine users with tuberculosis might remain contagious for longer periods. In addition, crack is often used in dwellings with limited ventilation to minimize detection, which may favour transmission.

Diphtheria. Sporadic outbreaks of non-toxigenic *Corynebacterium diphtheriae* strains have been reported in population subgroups such as homosexuals in Great Britain (Wilson, 1995), Aboriginals in Australia (Hogg *et al.*, 1996) and IDUs in Switzerland (Zuber *et al.*, 1992). The site of infection is often the skin rather than the pharynx and toxic manifestations are rare. A study from Zurich established a high carrier rate in drug users, with all *C. diphtheriae* isolates identified as biotype *mitis* and displaying the same restriction pattern by ribotyping (Gruner *et al.*, 1994). Gubler *et al.* (1998) reported a cluster of infections by nontoxigenic *C. diphtheriae mitis* among a group of Swiss drug users. Patients frequented the open drug scene ('needle parks') prevalent in Zurich at the time, which allowed easy access to drugs and the congregation of drug users from all over Europe. This clone and closely related ones have been recovered from cases of endocarditis and orthopaedic infections in IDUs from parts of Western Europe as well (Funke *et al.*, 1999). Given that migration and contacts are not uncommon among IDUs, it is possible that the strains may have spread through the use of common drug paraphernalia or through drugs themselves. Populations of IDUs can serve as a reservoir for *C. diphtheriae*, and given the propensity of non-toxigenic strains to cause invasive infections and acquire the toxin expressing lysogenic phage (McGregor, 2005); this reservoir could pose a serious public-health problem.

Viral infections

HIV. Drug use-related transmission accounts for at least 10 % of HIV infections globally, but this may have risen up to 40 % in recent times (Strathdee & Stockman, 2010), with injecting drug use taking over as the primary mode of HIV transmission in several countries. The sharing of needles/syringes and other drug-injection equipment is a well-known route of HIV transmission (Thompson *et al.*, 2003). However, injection drug use contributes to the spread of HIV even in non-drug user populations such as from IDU husbands to their non-injecting wives (Panda *et al.*, 2000). In Dar Es Salaam, Tanzania, local practices such as 'flashblood' (i.e. deliberate sharing of blood with drug preparations) may be fuelling HIV transmission, but the extent to which this or similar practices exist elsewhere is unknown (McCurdy *et al.*, 2010).

Non-injection drug use also contributes to the spread of HIV when users engage in risky behaviour such as trading sex for drugs or money. HIV prevalence estimates are similar for non-IDUs and IDUs across countries (Des Jarlais *et al.*, 2007; Bassols *et al.*, 2007; Strathdee *et al.*, 2008b) with several proposed explanations for the high prevalence in non-IDU populations (Strathdee & Stockman, 2010). Sharing of non-injection drug paraphernalia (straws, dollar bills used for snorting cocaine, inhalers and crack pipes) may play a role as drug users often have sores and cracks on their noses/mouths, which could facilitate viral transmission. The high degree of mixing or 'bridging' between IDU and non-IDU populations can lead to transmission of HIV through overlapping social and sexual networks.

The molecular epidemiology of HIV strains circulating among IDU populations is seen to correlate strongly with the prevalent regional subtype. However, a variety of recombinant forms have been seen to enter circulation leading to a growing complexity of HIV-1 strains (Sanders-Buell *et al.*, 2010; Mullick *et al.*, 2010; Ma *et al.*, 2009). Once introduced into IDU networks, these recombinant strains lead to an explosive rise in new HIV-1 infection, fuelled principally by needle sharing. In Manipur, the north-eastern state of India that borders Myanmar, rapid transmission of HIV infection among its vast drug-injecting population has been witnessed (Sarkar *et al.*, 1993). The seroprevalence among IDUs increased from 0 to 50 % within 6 months and the infection quickly spread to the population at large. Drug users continue to bear a substantial burden of HIV infection globally and interventions such as needle-exchange programs could reduce the likelihood of HIV transmission.

HBV and hepatitis D virus (HDV). Parenterally exposed groups such as drug users can easily contract and transmit HBV infection due to high-risk practices and the high HBV prevalence in this group (van Houdt *et al.*, 2009). Recent injecting is the main transmission route for HBV infection and though sexual transmission has become more important over time, it plays a minor role for transmission among IDUs (Levine *et al.*, 1995). Non-injecting drug users, on the other hand, are probably infected with HBV via unsafe sexual contacts and the sharing of crack-use equipment (Neaigus *et al.*, 2007). The majority of the drug users are infected with the identical genotype D strain, serotype ayw3 (Panessa *et al.*, 2009), which appears to be specific to this population. Sporadic spillover of HBV infection from the general population to the drug users via drug-injecting commercial sex workers and the reverse spillover from IDUs to the general population, via the heterosexual clients of drug-injecting commercial sex workers have been reported (van Houdt *et al.*, 2007, 2009). Combined HBV and HDV infection has been associated with hepatitis outbreaks with an unusually high mortality in drug users (Christensen *et al.*, 2001; Stevenson *et al.*, 2001). Though other routes of HDV acquisition such

as intrafamilial transmission have been reported, injecting drug use still remains the common route of transmission (Cross *et al.*, 2008).

HCV. Hepatitis C is the most common infection among IDUs, and at present IDUs form the major risk group for acquiring this infection. HCV prevalence rates in IDUs range from 40 to 90 % in different studies, and comprise up to 90 % hepatitis C notifications in certain countries (Thomas *et al.*, 1995; Jittiwutikarn *et al.*, 2006; Basu, 2010; Zamani *et al.*, 2010). Genotypes 1a and 3a predominate among IDUs, with genotype 3a being far more frequent in IDUs than the general population (Webster *et al.*, 2000; Silva *et al.*, 2010; Mahfoud *et al.*, 2010). A positive HCV status in IDUs is associated with the sharing of injection paraphernalia, frequency and years of drug use, HBV co-infection and alternate injecting practices, such as drawing blood into the syringe prior to injection (booting) (Hahn *et al.*, 2002; Stark *et al.*, 1997; Villano *et al.*, 1997). Drug abuse not only promotes HCV transmission but also plays a vital role as a cofactor in promoting HCV replication in host cells (Li *et al.*, 2003). In addition, primary HCV infection does not confer protective immunity against subsequent infection with viruses of other genotypes. Proust *et al.* (2000) report a case of two successive HCV infections in an IDU caused by two different HCV strains of genotypes 1a (first episode) and 3a (second episode). Even after clearance of the primary infection, IDUs are still at risk of acquiring a secondary HCV infection with a different viral genotype.

HTLV. Infection with proliferative HTLV I/II and cytopathic HTLV-III are known to be rare in the general population; however, IDUs engaging in practices such as needle sharing and 'booting' provide a setting highly favourable for transmission. IDUs are exposed to considerable antigen load due to the direct invasion of noxious chemicals, toxins and pathogens directly into their bloodstream. This predisposes them to rapid clinical progression to neurological (HTLV-I/II) or haematological (HTLV-I) disease.

The prevalence of HTLV infection in IDUs reveals a high degree of geographical variability. Robert-Guroff *et al.* (1986) reported seropositivity among IDUs in Queens, New York, to be 9 % for HTLV-I, 18 % for HTLV-II and 41 % for HTLV-III, which was significantly higher than that in the general population (less than 1 %). However, a study from South Scandinavia, which screened 693 IDUs, reported a prevalence rate as low as 0.7 % (Blomberg *et al.*, 1994). Prevalence rates also appear to vary considerably in the same country as well, ranging from 8.3 % in Brooklyn to 24.3 % in New Orleans in the USA (Lee *et al.*, 1990). While HTLV-II is the predominant strain among IDUs in the USA and Europe, a study from Israel reports predominant HTLV-I seropositivity among IDUs pointing to the possibility of an endemic focus of infection (Maayan *et al.*, 1992).

Fungal infections

While fungal infections in drug users are less common, systemic fungal infections such as cerebral abscesses and endocarditis may be fulminant and are associated with high mortality (Leen & Brett, 1991).

Candida species. Endogenous *Candida albicans* endophthalmitis in IDUs has been extensively documented in the literature (Aguilar *et al.*, 1979; Keyashian & Malani, 2007) and is one of the most common ocular complications of drug use. Culture recovery of *Candida* from the vitreous specimen is difficult and diagnosis largely relies on direct smear examination. Fruit juice is often used to dissolve drugs prior to injection and serves as a good culture medium for *Candida* (Albini *et al.*, 2007; Scheidegger *et al.*, 1993). Drug contamination by *Candida* is also associated with a distinct syndrome of disseminated infection characterized by chorioretinitis, folliculitis and costochondral arthritis (Odds *et al.*, 1987; Bisbe *et al.*, 1992).

Aspergillus species Though not as frequent as *Candida* species, fungal endophthalmitis caused by *Aspergillus* species is a recognized complication of drug use (Elliott *et al.*, 1979; Hirst *et al.*, 2005). Cases of *Aspergillus flavus* endophthalmitis among IDUs associated with unsterile injection practices, such as diluting drugs in tap water and filtering the mix through cigarette filters, have been reported (CDC, 1990). Because *Aspergillus* species are ubiquitous moulds, the source of infection is difficult to determine. Other forms of *Aspergillus* spp. infection such as osteomyelitis, endocarditis and brain abscess have also been associated with drug use (Salloum *et al.*, 2004; Petrosillo *et al.*, 2001; Morrow *et al.*, 1983).

Mucormycosis. Although isolated cerebral mucormycosis is uncommon, intravenous drug use is considered to be the most important risk factor associated with the infection. IDUs typically develop a form of primary cerebral mucormycosis affecting the basal ganglia and the *Rhizopus* species is most often isolated (Micozzi & Wetli, 1985; Verma *et al.*, 2006; Hopkins *et al.*, 1994). The infection probably results from parenteral inoculation of spores contained in the drugs or drug paraphernalia (Blázquez *et al.*, 1996). This entity differs from rhinocerebral zygomycosis commonly associated with diabetes mellitus with no external signs of involvement and deep CNS localization. In the presence of basal ganglia lesions in an IDU, the possibility of mucormycosis should be considered, regardless of the patient's HIV status (Gaing *et al.*, 1992).

Penicillium marneffei. *Penicillium marneffei* is an emerging fungal pathogen causing fatal systemic mycoses in immunocompromised patients. Endemic in tropical Asia, its importance as a human disease was recognized only after the arrival of the HIV pandemic. A report from Manipur, India, describes 36 cases of *Penicillium marneffei* infection in HIV infected individuals of which 31 (86%)

were IDUs (Ranjana *et al.*, 2002). Since the spread of HIV infection is closely linked to drug abuse, there is an increasing trend of *Penicillium marneffei* infection among IDUs. Drug abusers with a history of travel may serve as carriers of the infection and thus *Penicillium marneffei* infection should be considered in narcotic users even in non-endemic areas (Julander & Petrini, 1997; Viviani *et al.*, 1993).

Parasitic infections

Malaria. The earliest outbreak of malaria among IDUs was reported from the University of Cairo among heroin users linked with the communal use of syringes (Biggam, 1929). Since then there have been several reports describing epidemic outbreaks of malaria caused by *Plasmodium falciparum* and *Plasmodium vivax* traced to the sharing of needles among IDUs (Gonzalez Garcia *et al.*, 1986; Baker & Crawford, 1978; Brown & Khoa, 1975; Friedmann *et al.*, 1973; Bick & Anhalt, 1971). In fact, the mixing of quinine with heroin was a practice introduced by drug dealers in Chicago in the 1940s to halt an outbreak of malaria among IDUs (Platt & Labate, 1976).

The influence of narcotic addiction on the outcome of malaria in IDUs has been extensively studied (Chau *et al.*, 2002). Inoculation of 0.05 ml blood from a 'donor' with parasitaemia (~ 5000 parasites μl^{-1}) via an infected needle would exceed the number of parasites usually transmitted by a single mosquito bite. The consequences of a larger inoculum would be a shorter prepatent period and less time for specific host defences to be mobilized. This has led to the impression that malaria in IDUs is associated with a poor outcome. However, in the above study, the outcome of malaria in IDUs did not differ significantly from those who had acquired the infection via mosquito bite. Several factors such as malnutrition, iron deficiency and increased splenic function due to repeated infections may attenuate severe malaria in IDUs. The disadvantage of a large inoculum and short incubation period may be balanced by pre-existing immune defences. However, IDUs also potentially concentrate factors involved in the emergence and spread of drug-resistant strains such as treatment delay, immunosuppression and social marginalization (Bastos *et al.*, 1999).

Leishmaniasis. Needle sharing by IDUs has been proposed as providing an alternative, artificial and anthroponotic cycle for leishmania transmission. The prevalence of markers of leishmania infection (leishmanin skin test and serum leishmania antibodies) was reported to be higher among IDUs than among a similar cohort of individuals who were without a history of drug use (Pineda *et al.*, 2001). Arguments put forth in support of needle transmission of leishmania include the quantity of blood contained in a shared needle (~ 0.3 ml), which far exceeds the amount transmitted by the *Phlebotomus* bite (~ 0.3 – 0.5 μl), the patient's blood sample is capable of being infective to

sand-flies and that certain zymodemes are found almost exclusively in infected IDUs. Further, shared RFLP patterns were found in blood samples tested from discarded syringes in an outbreak of leishmaniasis in north-east Spain, suggesting the spread of certain leishmania clones among IDUs with shared needles as the vector (Cruz *et al.*, 2002).

Toxoplasmosis. The decline in Th1 and increase in Th2 activity, as a result of drug-induced immunomodulation, predisposes drug users to infection with intracellular pathogens such as *Toxoplasma gondii* (Buchy *et al.*, 2003; Li *et al.*, 2010). Cytokine investigations revealed reduced levels of phytohaemagglutinin-induced IFN- γ , serum IFN- γ and IL-12, but levels of IL-4, IL-6, IL-10 and TNF- α had concomitantly increased. IL-12 and IFN- γ production are essential for controlling infections caused by intracellular organisms, and IL-6 and TNF- α confer anti-*Toxoplasma* activity. The increase in IL-6 levels may provide a protective effect for the host by controlling the number of *T. gondii* parasites and also serve as a marker to assess infections with intracellular pathogens in IDUs.

Sexually transmitted diseases (STDs)

There is a long-standing relationship between STDs and illicit drug use. Up to 60 % of IDUs report a history of at least one episode of STD in the past (Nelson *et al.*, 1991) and high infection rates are also seen among non-IDUs, such as users of crack cocaine (Ross *et al.*, 2002; Williams *et al.*, 1996). The exchange of sex for money or drugs is common among drug users and is an independent risk factor for STD transmission (Astemborski *et al.*, 1994; McCree *et al.*, 2010). Stimulant drugs such as methamphetamine are also associated with enhanced sexual drive and paced mating behaviour (Holder & Mong, 2010). Localized high prevalence foci of syphilis in IDUs have important implications for the control of STDs, particularly HIV, in this group (Rolfs *et al.*, 1990; Ernst & Martin, 1993; Farley *et al.*, 1990). The role of needle sharing in syphilis transmission is yet to be resolved; however, a syringe prevalence of 6.9 % has been reported (Jose *et al.*, 1993; Abdala *et al.*, 2003). Drug abuse has also been significantly associated with other STDs such as gonorrhoea, chancroid, HSV-2, bacterial vaginosis, trichomoniasis and candidiasis (Fisher *et al.*, 2000; Ross *et al.*, 2002; Bastos *et al.*, 2000; Nguyen *et al.*, 2009). The substantial overlap between sex workers and IDU populations, and enhancement of HIV transmission by STDs, forewarns of large second-wave epidemics of sexually transmitted HIV infection among drug users (Aral & St Lawrence, 2002).

Conclusion

Infectious complications of drug abuse are frequently encountered in the hospital setting and constitute a major burden to the health-care system. The abuse of illegal drugs has the potential to adversely affect the immune response and increase susceptibility to infections. However, there is

convincing evidence that drug use-related practices also contribute to the increased exposure to pathogens. Special considerations should be given to issues in drug users such as polymicrobial infections (endocarditis), unusual forms of infection (isolated cerebral mucormycosis), unconventional routes of transmission (malaria transmitted via injection equipment), re-emergence of old diseases (tetanus), unfamiliar pathogens (*Paenibacillus larvae*), specific drug-infection associations (black tar heroin and wound botulism), atypical sites of infection (cutaneous diphtheria), outbreaks of rare infections (anthrax) and overlap syndromes (STDs). The activities of IDUs also promote the efficient transmission of blood-borne viruses such as HIV and HBV, and serve as an almost exclusive reservoir for HCV infection in the western world.

While antimicrobial therapy for drug use-related infections is essentially no different from that for the general population, the accurate identification and diagnosis of infections in drug users requires considerable skill. As laboratory physicians, microbiologists need to increase their knowledge base and expertise when dealing with infections in drug users, and enable laboratories with systematic diagnostic algorithms to address the special considerations of this population.

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