Review of management priorities for invasive infections in people who inject drugs: highlighting the need for patient-centred multidisciplinary care

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People who inject drugs (PWID) are a cohort at risk of invasive infections requiring hospitalisation. These infections include abscesses, bloodstream infections, infective endocarditis and bone and joint infections. There has been a significant rise in the prevalence of invasive infections related to injecting drug use (IDU) in the past 10 years.[1,2] Treatment of these infections can be complex, as it frequently requires prolonged antimicrobial therapy, management of substance use, mental health disorders, and social comorbidities, and can be complicated by challenging therapeutic relationships and stigma. Due to the spectrum of these infections and their presentations, PWID can be managed by many different clinical units in hospital, including medical, surgical and psychiatry. In this narrative review, we summarise current evidence on management strategies and highlight the priorities of care for PWID with invasive infections. This includes using a patient-centred multidisciplinary approach to engage and support PWID, individualised antimicrobial plans, and using the hospital admission as a time to address preventive strategies to decrease future risk of morbidity and mortality (Box 1).

Summary

- There has been a global increase in the burden of invasive infections in people who inject drugs (PWID).
- It is essential that patient-centred multidisciplinary care is provided in the management of these infections to engage PWID in care and deliver evidence-based management and preventive strategies.
- The multidisciplinary team should include infectious diseases, addictions medicine (inclusive of alcohol and other drug services), surgery, psychiatry, pain specialists, pharmacy, nursing staff, social work and peer support workers (where available) to help address the comorbid conditions that may have contributed to the patient's presentation.
- PWID have a range of antimicrobial delivery options that can be tailored in a patient-centred manner and thus are not limited to prolonged hospital admissions to receive intravenous antimicrobials for invasive infections. These options include discharge with outpatient parenteral antimicrobial therapy, long-acting lipoglycopeptides (dalbavancin and oritavancin) and early oral antimicrobials.
- Open and respectful discussion with PWID including around harm reduction strategies may decrease the risk of repeat presentations with injecting-related harms.

Methodology

We searched Ovid MEDLINE and EMBASE, PubMed and Google Scholar through to April 2022 for clinical trials, qualitative articles, reviews and clinical guidelines regarding to the care of invasive infections in PWID. Examples of search terms used include "injection drug use", "people who inject drugs", "endocarditis", "osteomyelitis", "skin and soft tissue infection", "outpatient parenteral antimicrobial therapy", "dalbavancin", "oritavancin", "addiction medicine", "opiate substitution treatment" and "stigma". We also manually searched the reference lists of identified articles for other relevant articles.

Engaging people who inject drugs in care

Acknowledging and addressing stigma

PWID frequently experience profound stigma from health care staff, and this significantly affects their engagement in care.[3] Negative attitudes towards PWID by health care staff can be the result of perceived risk of medication misuse, behavioural challenges, and poor motivation among PWID, combined with the perception that they themselves have had inadequate training to work with PWID.[3] Stigma towards PWID is associated with poorer health outcomes, including injecting-related harms and overdose, as well as delayed presentation to health care services and increased risk of unplanned discharges.[3,4]

Strategies to decrease stigma include educating health care providers regarding the importance of open and empathetic communication, respecting patient autonomy and improving clinician understanding of substance use disorders and harm reduction strategies. Education provided to clinicians on identifying key moments of infection prevention in injecting drug use was found to improve clinician comfort educating PWID.[5] Using a collaborative approach through multidisciplinary teams with peer support workers, if possible, acknowledging pre-existing bias and offering patient-centred management plans can also help reduce stigma.[6] Peer support workers for PWID are staff members who have a lived experience of a substance use disorder and can provide a unique level of support which is patient-centred.[6] Peer support workers have been demonstrated to increase retention in care, improve access to opioid agonist therapy (OAT), improve communication between PWID and health care workers, provide patient advocacy, and they can help coordinate care after discharge.[6,7]

Open discussions regarding substance use

Addiction is a chronic, relapsing-remitting disease that needs to be addressed to facilitate appropriate management of the invasive infection with which the patient has presented. Discussing substance use with patients in a non-judgmental manner can also help reduce stigma and improve engagement.

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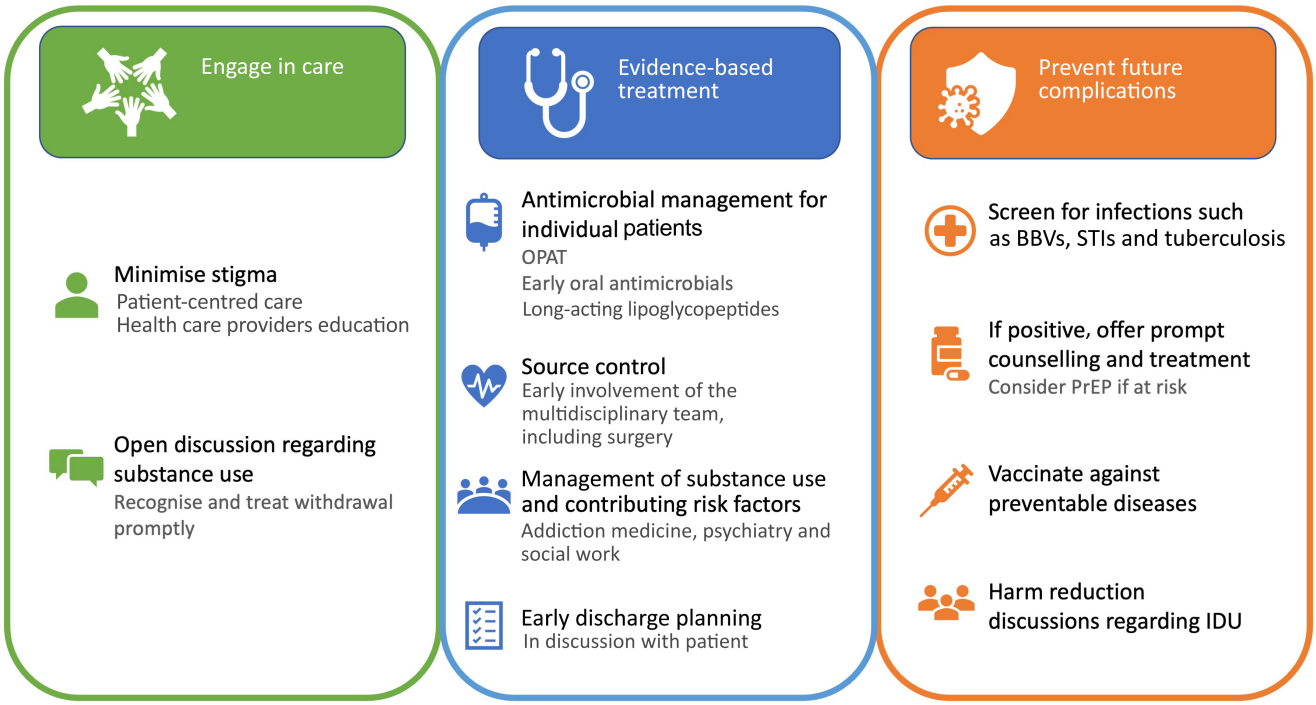
1 Priorities of care for people who inject drugs (PWID) admitted to hospital with invasive infections



BBV = blood-borne virus; IDU = injecting drug use; OPAT = outpatient parenteral antimicrobial therapy; PrEP = pre-exposure prophylaxis; STI = sexually transmissible infection.

The key components of a drug history are summarised in Box 2. This history not only forms part of the ongoing care plan for the patient, but also helps with a risk assessment of withdrawal. It is during the initial withdrawal phase when patients are at a heightened risk of using other substances to mitigate symptoms of withdrawal, as well as an increased risk of discharge in an unplanned manner. Understanding the patient's substance use is also essential to ensure appropriate pain management can be provided. This is particularly important as many invasive infections are complicated by acute pain. However, PWID often describe barriers to the receipt of adequate pain management, including clinician concern about "drug-seeking" behaviour.[4,8]

2 Components of a drug history in people who inject drugs admitted with an invasive infection

Components of a drug history:
- Drug used (including multiple substance use)
- Duration of drug use
- Frequency of drug use (including when a substance was last used)
- Quantity of substances used
- Routes of use
- Previous episodes of withdrawal or abstinence
- Previous episodes of treatment (including what has been trialled)

Common substances to screen for:
- Opioids (prescribed and not prescribed)
- Benzodiazepines
- Stimulants
- γ-hydroxybutyrate (GHB)
- Gabapentinoids
- Synthetic cannabis
- Cannabis
- Tobacco
- Vaping products
- Alcohol

Early referral to addiction medicine and pain services can help provide adequate analgesia to PWID which, apart from being an important therapeutic goal, is also a prerequisite for establishing a constructive therapeutic relationship.

Provision of evidence-based treatment for people who inject drugs with invasive infections

Antimicrobial therapy and delivery

Traditionally, invasive infections are treated with 2–6 weeks of intravenous antimicrobials.[9-12] Given injecting drug use is often a barrier to outpatient parenteral antibiotic programs, PWID with invasive infections frequently remain in hospital for prolonged periods of time.[13] However, there is emerging evidence that support strategies beyond traditional inpatient-based treatment for PWID with invasive infections. Here, we present the current evidence for these alternative approaches, which support the case for individual patient-centred decision making. It is beyond the scope of this review to discuss individual antimicrobial recommendations and, instead, we focus on the delivery of these antimicrobials.

Outpatient parenteral antimicrobial therapy

Outpatient parenteral antimicrobial therapy (OPAT) facilitates the delivery of intravenous antimicrobials to patients at home or in an OPAT clinic, permitting patients to return home rather than remain in hospital. Advantages of OPAT include greater patient satisfaction with care, the ability to return to usual daily activities including work, and reduced hospital length of stay, with associated cost savings for the health care institution.[14,15] There has traditionally been a resistance to enrolling PWID onto OPAT due to concerns about non-adherence, staff safety,

and tampering with central lines required for antimicrobial administration.[13] There are also no guidelines regarding the admission of PWID to OPAT, with the Infectious Diseases Society of America OPAT guidelines stating that "no recommendation can be made".[14] However, there is increasing evidence that PWID can be safely discharged on OPAT.

A literature review of ten studies assessing OPAT efficacy and safety among PWID which included a total of 800 individuals found completion rates of antimicrobials for PWID receiving OPAT ranged from 72% to 100%, comparable to completion rates in other patients.[15,16] Rates of central line tampering are low in available studies (0–2%),[17-19] and no significant difference in rates of line infections have been noted.[20,21] While PWID may require more intensive support when receiving OPAT (including increased after-hour nursing calls),[21] staff safety has been demonstrated.[22]

Intermittent injecting drug use should not be used as a definitive dismissal criterion from OPAT, with studies demonstrating OPAT success with patients who have continued to inject.[18,23] Instead, admission criteria onto OPAT should be individualised and consider patient clinical stability and the availability of an appropriate antimicrobial management plan that is able to be delivered via OPAT. Social instability leading to a decreased ability to return for treatment should be considered. The authors of a 2017 study found that 41 of 67 PWID (61%) enrolled in OPAT failed treatment when single missed antibiotic doses or clinic appointments were defined as failure of OPAT treatment.[17] However, this should be balanced with the risk of complete disengagement from inpatient treatment compared with potential longer term engagement with an outpatient model and individual supports through a multidisciplinary team.

Oral antimicrobials for serious infections

There has recently been a reinvigorated debate regarding the use of early oral antimicrobials for invasive infections traditionally managed with prolonged intravenous therapy.[24] Two large randomised clinical trials published in 2019 provided evidence regarding the efficacy and safety of early oral antibiotic therapy to complete treatment for infective endocarditis and bone and joint infections.[25,26] However, these trials are difficult to extrapolate to PWID, as PWID were either not included or were only 1% of the oral treatment arm.[25,26] Data on oral antibiotic treatment for invasive infections in PWID are limited and mainly rely on retrospective studies in populations without a history of injecting drug use.[27]

An important consideration in the use of oral antimicrobials is the potential for clinically relevant drug interactions. Early oral antimicrobial therapy for invasive infections usually relies on agents with high bioavailability, such as rifampicin, ciprofloxacin and linezolid. These antimicrobials can interact with other medications (including OAT) and recreational drugs.[27] Pharmacists should be involved in care teams early to provide dispensing advice and review any potential interactions in conjunction with addiction medicine and pain services. Box 3 provides a summary of some key interactions that may be experienced in the management of PWID with oral antimicrobials. It is also important to consider when the interacting drug is stopped and the need for medications to return to their baseline dose (eg, if rifampicin is used with methadone). At present, there is scant evidence about the comparative effectiveness of early oral antibiotics compared with standard intravenous therapy among PWID with invasive infections. Oral antimicrobials should not be used simply to facilitate an earlier discharge, especially if this would not be standard of care for people without a substance use history. If oral antimicrobials are to be used, a clear management plan with close follow-up should be implemented to mitigate the risk of non-completion and loss to follow-up.

Long-acting lipoglycopeptides

Lipoglycopeptides, such as dalbavancin and oritavancin, are parenteral antibiotics with long half-lives that achieve high concentrations in bone, skin and synovium.[29-31] Dalbavancin can be dosed once weekly thanks to its half-life of 147–258 hours, while oritavancin can be dosed once per treatment course for gram-positive infections due to its half-life of 245–393 hours.[30,32] These agents have therefore been suggested as potential management strategies for PWID to provide intravenous antibiotics without the need for prolonged inpatient hospitalisation or OPAT admission.

The United States Food and Drug Administration approved dalbavancin in 2014 and oritavancin in 2015 for the treatment of skin and soft tissue gram-positive bacterial infections.[32,33] There has been increasing interest in the off-label use of these agents for invasive infections, including in populations who may not be suitable OPAT candidates such as PWID. While current studies are heterogenous regarding the infections treated (including bacteraemia, infective endocarditis, and bone and joint infections), as well as the dosing used, treatment success rates range from 64% to 100%.[34-44] Many studies have also demonstrated that these lipoglycopeptides can be successfully used in PWID.[36,40,41,44,45] While predominantly retrospective in nature, no significant difference in clinical success and adverse events in PWID subgroups has been found.[41,44,45] The spectrum of activity and success in available studies suggest that these agents may have a role to play in the management of invasive infections in PWID. Current limitations of these lipoglycopeptides in the Australian setting include the cost (roughly $1850 per 500 mg vial of dalbavancin) and that they are accessed through the Therapeutic Goods Administration Special Access Scheme and thus need to be imported from overseas, with the associated time lag. However, potential advantages include an alternative to oral therapy and OPAT where there are barriers to these options, earlier discharge from hospital, and decreased health care costs.[39] Furthermore, PWID are becoming increasingly familiar with long-acting preparations thanks to the implementation of long-acting injectable depot buprenorphine.[46] The increasing use of these agents could also allow for the co-administration of dalbavancin or oritavancin in outpatient settings with weekly depot buprenorphine, again increasing engagement of PWID.

Antimicrobial delivery

Despite increasing evidence for alternative strategies such as OPAT and long-acting lipoglycopeptides for invasive infections, the default approach for PWID is frequently prolonged inpatient intravenous antimicrobials.[13] This should no longer be the default position, as there is increasing evidence that PWID can be discharged safely to an OPAT service with appropriate supports. However, if patients are not able to be managed on OPAT, dalbavancin and oritavancin offer promise as alternatives. The widespread use of these agents is currently limited due to their high cost and lack of availability and predominantly retrospective evidence base. Upcoming randomised controlled trials, such as the DOTS trial (https://clinicaltrials.gov/ct2/show/NCT04775953) assessing dalbavancin efficacy, will strengthen knowledge around their role. Oral antimicrobials may be considered as an alternative option, with close review

3 Interactions between opioid agonist therapy, diazepam and common antimicrobials used in invasive infections

Class	Medications	Interaction	Effect	Pharmacology	Recommendation	Evidence
Azoles	Fluconazole, itraconazole, posaconazole, voriconazole	Methadone	Methadone toxicity increased. Combination may lead to additive risk of QT prolongation	Azoles inhibit CYP3A4-mediated metabolism of methadone, and may increase serum levels	Fluconazole and voriconazole: use with caution; monitor for methadone toxicity. Regular ECGs recommended	Case reports and small studies
					Itraconazole and posaconazole: avoid combination	
		Buprenorphine	Buprenorphine toxicity may be increased	Azoles inhibit CYP3A4-mediated metabolism of buprenorphine, and may increase the serum levels	Use combination with caution; monitor for signs of buprenorphine toxicity and reduce the dose as necessary. Sublingual route buprenorphine has the highest theoretical risk of interaction	Theoretical and case reports
		Diazepam	Diazepam sedative effects may be increased	Azoles may inhibit diazepam's CYP2C19- and/or CYP3A4-mediated metabolism, and may increase its serum concentration	Use combination with caution; monitor for signs of toxicity and decrease diazepam dose if necessary	Case reports and small studies
Rifamycins	Rifampicin, rifabutin	Methadone	Methadone effect may be reduced	Rifamycins have been demonstrated to significantly reduce serum levels by inducing hepatic CYP3A4-mediated metabolism	Use combination with caution; monitor for opioid withdrawal. May need to increase methadone dosage to avoid withdrawal symptoms. Interaction more likely with rifampicin compared with rifabutin	Case reports and small studies
		Buprenorphine	Buprenorphine effect may be reduced	Rifamycins may induce buprenorphine's CYP3A4-mediated metabolism and may reduce its serum concentration	Use combination with caution; monitor patient clinically for opioid withdrawal. Increase buprenorphine as necessary to avoid withdrawal symptoms. Interaction more likely with rifampicin compared with rifabutin	Case reports and small studies
		Diazepam	Diazepam serum level may be reduced	Rifampicin induces diazepam's CYP3A4-mediated metabolism and may reduce its serum concentration	Use combination with caution; monitor patient clinically. Adjust dosage of diazepam if loss of efficacy	Case reports and small studies
Fluroquinolones	Ciprofloxacin, moxifloxacin	Methadone	Risk of additive toxicity and prolonged QT causing potentially life-threatening torsade de pointes	Both quinolones and methadone prolong the QT interval. Moxifloxacin has the most pronounced effect on QT	Moxifloxacin: avoid combination	Theoretical and case reports
					Ciprofloxacin: use with caution; regular ECG monitoring recommended	
Macrolides	Azithromycin, clarithromycin	Methadone	Risk of additive toxicity and prolonged QT causing potentially life-threatening torsade de pointes	Both macrolides and methadone prolong the QT interval	Clarithromycin: avoid combination	Theoretical and case reports
					Azithromycin: use with caution; regular ECG monitoring recommended	
		Buprenorphine	Buprenorphine serum concentration may be increased	Macrolides inhibit buprenorphine's CYP3A4-mediated metabolism and may increase its serum concentration	Use combination with caution; monitor for signs of drug toxicity	Theoretical
Oxazolidinone	Linezolid	Methadone	Risk of additive effect and increased risk of serotonin syndrome	Methadone and linezolid both have serotonergic properties. If more than one serotonergic agent is used (eg, SSRI, cocaine, MDMA), there is increased risk of serotonin syndrome	Use combination with extreme caution; monitor for symptoms of serotonin syndrome and cease concurrent treatment if serotonin syndrome occurs	Theoretical

ECG = electrocardiogram, MDMA = 3,4-Methylenedioxymethamphetamine; SSRI = selective serotonin reuptake inhibitor. Orange colour = use combination with caution; red colour = avoid combination. Data synthesised and adapted from MIMS Online (www.mimsonline.com.au), Australian Medicines Handbook Online (https://amhonline.amh.net.au/auth) and Stockley's Drug Interactions.[28] The references supporting the level of evidence provided are listed in the Supporting Information.

of all (prescribed and non-prescribed) pharmaceuticals used to ensure no significant drug interactions will occur. In summary, there are a range of options for the delivery of antimicrobials for PWID with invasive infections, and each case must be considered on its own merit to ensure the best patient-centred plan is delivered.

Ensuring source control

Antimicrobials are only one component of the successful management of invasive infections. Source control of the infection is required to ensure resolution. However, many barriers remain for PWID to receive surgery. In the case of infective endocarditis, it has traditionally been recommended to avoid surgical management in PWIDs.[9,10] However, evidence regarding operative outcomes in IDU-infective endocarditis is increasing and individual patient-specific surgical management should be considered.

Similar, or lower, operative mortality and no significant difference in early postoperative mortality has been demonstrated between IDU-infective endocarditis and infective endocarditis not related to IDU.[47-50] A recent meta-analysis demonstrated no significant difference in in-hospital mortality (risk ratio [RR], 0.88; 95% CI, 0.51–1.54) nor in 30-day mortality (RR, 0.77; 95% CI, 0.36–1.64).[47] This contrasts to studies of mid- and long term outcomes following surgery, which have demonstrated poorer outcomes in PWID, contributed to by an increased risk of reinfection.[48,51-53] Survival rates following surgery for IDU-infective endocarditis in an observational cohort study in Sweden over 17 years demonstrated a 49% 5-year survival in patients who had IDU-infective endocarditis compared with 76% in those without a history of injecting, and a higher risk of reoperation (adjusted hazard ratio, 3.47; 95% CI, 1.74–6.89; $P < 0.001$).[48] Overall, these studies demonstrate that PWID can tolerate surgery well and, thus, should be considered for appropriate source control when required. However, the longer term outcomes are complicated due to the increased risk of reinfection. This again indicates the importance of comprehensive care including addressing substance use and addiction during the admission for an IDU-related invasive infection. Multidisciplinary teams are recommended in guidelines for the management of infective endocarditis[9,10] and contribute to improved outcomes in patients.[54,55] For PWID, these teams should include not only surgical and medical staff but also addiction medicine, psychiatry, anaesthetics, social work, nursing and peer support as well as the patient themselves so an individualised plan can be made. These teams require collaboration and a willingness to re-evaluate practices by all specialties and should be spearheaded by change-makers at institutions to drive their initiation.[56] We argue that there should be no defined exclusions to patients receiving surgery, instead the patient and their multidisciplinary team should make an informed decision assessing both medical and psychosocial factors of the individual case at hand.

Management of substance use and psychosocial comorbidities

As well as providing treatment for the invasive infection, an evidence-based assessment and treatment model should be included for the underlying substance use. Linkage with addiction medicine or alcohol and other drug services is associated with improved outcomes for PWID. This includes increased uptake of OAT, antimicrobial completion, reduced readmission and reduced mortality.[57-59] Use of OAT by PWID not only reduces illicit opioid use but also overdose risk, injecting related illness including blood-borne virus transmission, readmission rates, retention in care, and all-cause mortality.[58,60] However, despite documented benefit, hospitalised patients with substance use disorders often have low and delayed referrals to addiction teams and OAT.[61,62] Where available, early referral is an essential part of the multidisciplinary care of PWID. Addiction teams are also crucial in supporting patients with stimulant use disorders (such as methamphetamine use), given the variety of use patterns, available preparations, intoxication presentations and potential for prolonged withdrawal period. Referral to addiction medicine should also continue in the post-discharge period, as there is an increased risk of injecting harms, including overdose, in the period immediately following discharge from hospital.[63]

Addiction medicine and psychiatry colleagues can also play an important role in educating clinicians regarding addiction and the interplay with past trauma and psychosocial comorbidities on behaviour and engagement. This is particularly important as PWID experience an increased rate of comorbid conditions such as mental health disorders and previous trauma.[64] PWID also frequently experience multiple social stressors, including unstable housing, job instability, legal and domestic disputes, which can all negatively affect mental health and substance use risk.[64] These comorbid conditions need to be addressed and supported to effectively engage patients and manage their infective complications of IDU. Services including psychiatry, pain specialists, social work and community care, as well as addiction medicine, are thus crucial team members to ensure the adequate acute support of PWID and decrease the longer term risks of injecting-related harms.[64]

Early discharge planning

PWID have higher rates of unplanned discharge than non-IDU patients admitted for the same infective conditions, with a prevalence range of 25–30%.[65,66] Unplanned discharge is linked with higher 30-day mortality, readmission and longer subsequent hospital stays.[67,68] Rather than reflecting non-compliance on the side of the patient, unplanned discharge has more recently been reframed as a failure of the health service to provide a supportive health care environment within which the needs of patients admitted to hospital with IDU, including addiction, mental health and social stressors, are not met.[67] An emergency oral antimicrobial plan (including take-home naloxone) that can be enacted if a patient decides to discharge earlier than advised can help decrease readmission rates and morbidity.[69] Efforts should also be made to provide the patient with outpatient follow-up with infectious diseases specialists or their local doctor, even if they have an unplanned discharge.

Hospital admission as an opportunity for prevention

Screening

There are higher rates of sexually transmissible infections, viral hepatitis, human immunodeficiency virus (HIV) infection, and tuberculosis seen in PWID than non-PWID.[70] Hospital admission can provide the opportunity for PWID, who may not be receiving regular health care, to be screened for these conditions. If positive results are returned, patients should be provided with counselling about the benefits of rapid initiation of therapy, especially for hepatitis C and HIV infection.[70] Men who have sex with men and who are negative for HIV infection

should also be provided with information about HIV pre-exposure prophylaxis as well as regular sexually transmissible infection screening.[71]

Vaccination

Hospitalisation can also be a time to review protection against vaccine-preventable diseases. In PWID, this includes hepatitis A and B, influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and tetanus if there is no evidence of immunity or the recommended vaccine guidelines have not been met.[70] Pneumococcal vaccines should also be considered if eligible.

Safer injecting practices

Safer injection techniques should be discussed, such as injection site preparation and use of filters and sterile water, where possible, and use of sterile needles and syringes, including not reusing needles.[70] Overdose prevention education, such as naloxone information for people who inject opioids, should also be provided, as well as provision of community resources for addiction treatment and the availability of medically supervised injecting rooms. While naloxone is currently available in Australia, there is low access and training with naloxone among Australian PWID.[72] Hospital admission thus provides an opportunity to provide take-home naloxone and associated training, which can thereby also increase accessible naloxone in the community. By promoting harm reduction during admissions, PWID may feel less stigma and judgement, which in turn improves overall engagement in treatment and reduced risk of subsequent admissions with IDU-related infections.

Conclusion and future research

The management of invasive infections in PWID can be challenging for both patients and clinicians due to the requirement of prolonged antimicrobials and the demands of complex comorbid conditions. Much of the current evidence is driven by retrospective studies, and prospective trials are required to provide strengthened evidence regarding the optimal management of invasive infections in PWID. A prospective multicentre cohort study is currently enrolling in Australia to assess the outcomes of varied management options of PWID admitted to hospital with invasive infections.[73] A randomised controlled trial is recruiting in Canada to assess oral antimicrobials for PWID with infective endocarditis (https://clinicaltrials.gov/ct2/show/NCT04544306?draw=2), while an international randomised adaptive clinical trial assessing interventions for *Staphylococcus aureus* bacteraemia will include a subanalysis of PWID (https://clinicaltrials.gov/ct2/show/NCT05137119).[74]

The prevalence and diversity of invasive infections in PWID often requires a wide range of health care teams to provide care for these patients. Thus, the use of multidisciplinary teams can not only support patients, but clinicians as well. There is increasing evidence that PWID do not need to remain hospitalised for prolonged periods due to an invasive infection and, therefore, early discussions regarding discharge planning should occur with patients. Applying early use of a multidisciplinary, pragmatic, patient-centred, non-judgemental approach may allow these patients to not only achieve improved outcomes for their invasive infections but also reduce their risk of subsequent admissions.

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Supporting Information

Additional Supporting Information is included with the online version of this article.