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Applying the Infectious Diseases Literature to People who Inject Drugs

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INTRODUCTION

Increasing rates of opioid use disorder have resulted in an epidemic of infectious complications of injection drug use (IDU). This includes outbreaks of human immunodeficiency virus (HIV)[1] and hepatitis C virus (HCV),[2] as well as increasing hospitalizations from skin and soft tissue infections (SSTIs), osteomyelitis, septic arthritis, bacteremia, central nervous system infections, and endocarditis.[3-7] Despite increasing incidence of IDU-associated infectious diseases, the best approach to management is unclear, varies widely, and remains understudied.[8-10] There is a critical need to identify the best ways to care for patients with IDU-associated infections.

To answer questions about the treatment of patients with IDU-associated infections, clinicians are tasked with applying the best available evidence, yet this research has often excluded people who inject drugs (PWID). Over the past few years, the literature has provided some answers to many of the fundamental questions in infectious diseases (IDs). With increased interest in evidence-based medicine, funding for pragmatic clinical trials, and democratization of the medical literature through social media, many long-held dogmas have been reversed based on robust clinical data. Examples include studies showing noninferiority of oral versus intravenous (IV) antibiotics for certain severe infections,[11,12] shorter versus longer courses of antibiotics,[13] and bactericidal versus bacteriostatic antibiotics.[14] Care must be taken when applying the ID literature to PWID. In this article, the authors will first describe important differences between PWID and the general population represented in

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clinical trials. Next, they propose an approach to using the literature to inform the management of IDU-associated infections. The authors then apply these principles to important evidence-based practices and provide a framework for designing effective treatment plans for PWID with severe infections.

DIFFERENCES BETWEEN PEOPLE WHO INJECT DRUGS AND PATIENTS REPRESENTED IN CLINICAL TRIALS

Recognizing differences between PWID and patients typically represented in clinical trials is important to appropriately contextualize these data for patients with IDU-associated infections. Table 1 describes unique attributes of PWID and implications of how these differences from the general population may affect infection-related outcomes. Table 2 presents common drug-drug interactions relevant to PWID presenting with IDU-associated infections.

APPLYING EVIDENCE-BASED PRACTICES TO INJECTION DRUG USE-ASSOCIATED INFECTIONS

In order to apply the ID literature to PWID, the authors suggest answering 3 questions about each evidence-based practice considered:

What is the evidence for this practice in the general population?

What is the evidence for this practice specifically among PWID?

What are the risks, benefits, and implications for applying this practice to PWID?

The focus of this article is on management questions in the treatment of severe IDU-associated infections requiring hospitalization (Table 3). The purpose of this article is not to provide a comprehensive guide to the management of all IDU-associated infections, but rather to build a framework for applying the best available evidence to a vulnerable population in a thoughtful and informed manner.

OUTPATIENT PARENTERAL ANTIMICROBIAL THERAPY FOR INJECTION DRUG USE-ASSOCIATED INFECTIONS

Evidence for Outpatient Parenteral Antimicrobial Therapy in the General Population

Outpatient parenteral antimicrobial therapy (OPAT) allows patients to receive IV antimicrobials outside of the acute care hospital setting. Patients receiving OPAT usually require placement of a peripherally inserted central catheter (PICC) to facilitate antimicrobial infusions, either at home, in a skilled nursing facility (SNF), nursing home, or other institution. OPAT has been deemed safe and effective for a variety of severe infections, including endocarditis.[15,16] The 2018 Infectious Diseases Society of America OPAT guidelines enumerate the benefits of OPAT, which include decreased hospital lengths of stay, reduced health care costs, fewer hospital acquired infections, and increased patient satisfaction, when compared with completing hospital-based antimicrobial therapy (HBAT).

[15] Yet, although there are definite benefits to OPAT overall, the harms have been less well-defined.[17] For one of the most common OPAT indications, *Staphylococcus aureus* bacteremia, Townsend and colleagues[18] documented an adverse event rate of 33% and 90-day readmission rate of 64% among patients receiving OPAT; however, there was no comparison to a group receiving HBAT. OPAT has become standard of care for most infections requiring an extended period of IV antimicrobials, and it is supported by strong evidence.

Evidence for Outpatient Parenteral Antimicrobial Therapy Among People Who Inject Drugs

Guidelines do not explicitly make a recommendation for or against providing OPAT to PWID, but recommend evaluation on a case-by-case basis.[15] However, many individual OPAT programs, home infusion companies, and hospitals have guidelines prohibiting OPAT for patients with a history of substance use disorders (SUDs) and PWID in particular.[9,10,19] Suzuki and colleagues[20] performed a review of published OPAT cohorts including PWID. Successful completion of OPAT ranged from 72% to 100% among studies reporting this outcome. Among studies that directly compared PWID versus OPAT among other patients, differences in treatment failure, readmission, mortality, and reinfection rates were negligible. PICC complications ranged from 3% to 9% across the cohorts, although some programs utilized special tamper-proof devices and frequent nurse oversight that might not be standard of care or available in most OPAT programs. Among studies comparing PICC complications between PWID and other patients, there were no significant differences. Patients were discharged to a mix of home, SNF, medical respite programs, and substance use rehabilitation programs. Home OPAT had no worse outcomes than those completing OPAT in an SNF, and patients have far better experiences with home OPAT versus SNF.[21,22]

There is reason to believe that treatment of the underlying SUD, especially in the case of OUD, has major implications for the success of OPAT among PWID. In a pilot randomized controlled trial for patients with OUD requiring IV antibiotics, all received treatment with buprenorphine, and those randomized to home OPAT had equal success to those receiving HBAT.[23,24] In 1 health system, an IV antibiotic risk score was implemented to assess addiction disease activity to guide OPAT decisions.[25] Using this score, low-risk patients were eligible to complete antibiotic outside the hospital, which reduced mean hospital stay by 20 days.

Applying Outpatient Parenteral Antimicrobial Therapy Data to People Who Inject Drugs

One of the key determinants in considering the implementation of OPAT for PWID is the expected efficacy of the alternatives to OPAT. In this section, the authors presume that the IDU-associated infection in question requires at least daily doses of IV antibiotics. In such cases, the alternative to OPAT is prolonged hospitalization for HBAT. Prolonged hospitalizations for PWID can be traumatic and an antitherapeutic experience.[26] These hospital stays are marked by untreated withdrawal, undertreated pain, stigmatization by health care providers, and subjection to restrictions on mobility off the ward.[27-29] Early discharge (against medical advice or AMA) is common among patients receiving HBAT, often without any antibiotics or medical follow-up, and is associated with increased mortality.[30-32] For patients who remain in the hospital, prolonged hospitalization can be a

reachable moment and opportunity to initiate evidence-based therapies for SUDs.[27,33] However, addiction as the underlying cause of disease often goes unacknowledged and untreated.[30,34-37] OPAT is an effective intervention overall; success is possible among PWID, and the alternative to OPAT can be harmful and costly to patients. Effectiveness of OPAT for PWID depends on the individual patient's SUD, access to addiction treatment (including medication for opioid use disorder [MOUD], when indicated), and SNF and home infusion company acceptance of PWID receiving OPAT/MOUD.[38]

ORAL ANTIBIOTICS FOR INJECTION DRUG USE-ASSOCIATED INFECTIONS

Evidence for Oral Antibiotics for Severe Infections in the General Population

Dogma has long dictated that severe bacterial infections should be treated with IV antibiotics. The preference for IV over oral antibiotics has been especially pervasive for osteomyelitis and endocarditis, yet recent studies have shown noninferiority of oral versus IV antibiotics for common severe infections among PWID. Many of these studies focus on the use of antibiotics with high oral bioavailability or combination therapy including at least 2 agents with differing mechanisms of action. Schrenzel and colleagues[39] compared a fluoroquinolone/rifamycin combination versus flucloxacillin or vancomycin for severe staphylococcal infections, excluding left-sided endocarditis, and showed noninferiority of the oral regimen. There are multiple retrospective studies showing noninferiority of early switch to oral antibiotics—primarily linezolid—for uncomplicated SAB and other severe *S aureus* infections; however, they are prone to selection bias and should be confirmed by prospective studies.[40-42]

Two recent randomized controlled trials (RCTs) for the treatment of endocarditis and osteomyelitis have led to wider adoption of oral antibiotics for severe infections. The POET (Partial Oral Treatment of Endocarditis) trial compared an early switch to oral antibiotics for patients with left-sided endocarditis caused primarily by methicillin-sensitive *S aureus* (MSSA), *Streptococcus species*, and *Enterococcus species*.[11] Patients with minimal valve complications were randomized to switch to oral combination therapy after at least 10 days of IV therapy or to continue on IV. The composite outcome rates were 12% in the IV arm and 9% in the oral arm, consistent with noninferiority. Long-term follow-up continued to show noninferiority of oral therapy.[43] The OVIVA (Oral Versus Intravenous Antibiotics) study was a pragmatic clinical trial comparing oral versus IV therapy for bone and joint infections performed in the United Kingdom. Patients were randomized to oral or IV therapy after less than 7 days of IV lead-in. Treatment failure at 1 year was noninferior between the 2 arms (15% IV vs 13% oral), with more catheter-related complications in the IV group.

Evidence for Oral Antibiotics for Severe Infections Among People Who Inject Drugs

Studies of oral antibiotics for severe infections among PWID date back to the late 1980s but have not been rigorously studied in the modern era. The first attempt at using oral therapy for right-sided *S aureus* endocarditis was documented in 1989 when a cohort of 14 patients were treated with ciprofloxacin and rifampin for 4 weeks.[44] An RCT of oral versus IV therapy for right-sided endocarditis among PWID published in 1996 showed noninferiority

of oral therapy; few patients, however, had MRSA, and all remained inpatient despite receiving oral therapy.[45] Of the high-quality RCTs noted previously, few included any PWID (POET included 5 PWID) or otherwise did not report on the number of patients with SUDs (OVIVA). In an observational study of oral versus IV therapy for MRSA bacteremia, 20% (N = 99) were PWID, of which 22 received oral antibiotics.[41] Subgroup analysis of these 99 patients was not reported, but of the 5 total failures in the oral group, 2 were PWID. In sum, there is minimal contemporary data comparing outcomes of oral versus IV therapy among PWID for severe IDU-associated infections.

Applying Oral Antibiotic Data to People Who Inject Drugs

The potential benefits of oral therapy for PWID include shorter hospitalizations, more freedom, and lack of PICC-related complications. Although there is robust evidence to support the use of oral antibiotics for bone/joint infections and endocarditis, there are a few important limitations in applying these data to PWID. The use of long-term IV antibiotics often comes with weekly clinical follow-up and monitoring that might be lacking in the real-world application of oral antibiotics to PWID. In POET, patients receiving combination oral antibiotics were seen up to 3 times weekly with close follow-up of response to therapy. The health care contact that comes along with HBAT and OPAT (eg, home health nurse visits) might lead to greater adherence to IV than oral therapy. Data supporting oral antibiotics for severe infections should be applied to PWID with caution and are not a license to discharge patients with pills and minimal follow-up plans.[46] Another consideration is that oral antibiotic regimens may have more potential drug interactions relevant to PWID including the common use of rifamycins in many well-studied oral regimens (see Table 2). OVIVA and POET included few patients with MRSA infection, which is common among PWID in the United States.[47] Similarly, many studies used fluoroquinolone combination therapy, to which there is increasing resistance among *S aureus* isolates worldwide.[48] The use of oral antibiotics for severe infections among PWID is promising and can be successfully implemented, but should include shared decision making with patients, with consideration of their social situation and addiction treatment options, rather than being a 1-size-fits-all approach.

Shorter-Course Antibiotics for Injection Drug Use-Associated Infections

Increasing evidence supports the idea that traditional lengths of antibiotic therapy can be shortened substantially without compromising outcomes and with fewer antibioticrelated adverse events.[13,49,50] Most of these data have been accrued for pneumonia, urinary tract infections (UTIs), cellulitis, gram-negative bacteremia, and intraabdominal infections, with few rigorous clinical trials evaluating short-course therapy for infections typical among PWID, such as osteomyelitis and endocarditis. A systematic review and meta-analysis of treatment length of osteomyelitis—more than half were pediatric patients—showed noninferiority of shorter course overall, with an odds ratio of 1.50 (95% confidence interval [CI] 0.97-2.34) for treatment failure; however, subgroup analyses indicated some important differences.[51] Patients with *S aureus* infections and those with vertebral osteomyelitis had more treatment failure when given less than 4 to 6 weeks of antibiotics. There was also no subgroup analysis of adult-only trials, which severely limits adaptation to PWID. An RCT of 2 versus 4 weeks of antibiotics for primarily small-joint septic arthritis showed

noninferiority of a short course, as did a comparison of 6 versus 12 weeks for pyogenic vertebral osteomyelitis.[52,53] In contrast, a prospective observational study of treatment for hematogenous vertebral osteomyelitis showed decreasing relapse with increasing length of treatment, especially among patients with MRSA infection and undrained abscesses.[54]

Evidence for Shorter Course Antibiotics for Severe Infections Among People Who Inject Drugs

Studies of short- versus longer-course antibiotics have almost systematically not included PWID. The only 2 studies specific to PWID evaluate a shorter antibiotic course of combination therapy including an aminoglycoside for right-sided *S aureus* endocarditis without a longer-course comparator.[55,56] Chambers and colleagues[55] performed a prospective study and administered 2 weeks of nafcillin (N = 50) or vancomycin (N = 3) both with tobramycin to 53 PWID. They found 94% and 33% (N = 1) cure rates with nafcillin and vancomycin, respectively. Ribera and colleagues[56] performed an RCT among PWID to compare cloxacillin with versus without gentamicin for right-sided MSSA endocarditis. Cure rates were similar between the 2 groups (86%–89%, $P>.2$), indicating high success with short-course cloxacillin monotherapy. Of studies in the general population, only the study by Gjika and colleagues (2 vs 4 weeks for native joint septic arthritis) made mention of inclusion of PWID (N = 9 out of 154).

Applying Shorter-Course Antibiotic Data to People Who Inject Drugs

In comparison to data on oral versus IV antibiotics, the shorter- versus longer-course literature is more readily adaptable to PWID. The main caveat is that most of the data on management of osteomyelitis and septic arthritis were predicated on appropriate source control procedures. PWID with more complicated infections or multifocal infections with incomplete surgical management would call into question the applicability of shorter-course approaches. Apart from native joint septic arthritis with surgical drainage, the bone/joint literature dictates 4 to 6 weeks of antibiotics for most infections, and this seems appropriate to apply to PWID. Based on the prospective study by Park and colleagues,[54] it would be reasonable to extend treatment of hematogenous vertebral osteomyelitis to longer than 6 weeks, especially in the setting of MRSA or undrained abscesses, which might be more common scenarios among PWID. As with the oral versus IV discussion, appropriate treatment of any infection requires follow-up and monitoring for response to treatment. Whether shorter or longer courses of antibiotics are used, access to postacute care ID services is crucial and ideally could be colocalized with management of the patient's SUD.[57]

LONG-ACTING INTRAVENOUS ANTIBIOTICS FOR INJECTION DRUG USE-ASSOCIATED INFECTIONS

Evidence for Long-Acting Intravenous Antibiotics in the General Population

Dalbavancin and oritavancin are long half-life lipoglycopeptide antibiotics dosed once weekly intravenously for gram-positive infections, obviating the need for daily infusions or PICCs. Both are approved by the US Food and Drug Administration (FDA) for the treatment of SSTIs, but have been increasingly used off label for treatment of other infections. Two

phase 2 RCTs have evaluated the efficacy of dalbavancin for non-SSTIs. Raad and colleagues[58] compared dalbavancin for 2 weekly doses versus 14 days of vancomycin for central line-associated blood stream infections. Dalbavancin was statistically superior to vancomycin (success rate of 87% vs 50%, $P<.05$), but numbers were small (N = 67); no power calculation was presented, and the vancomycin arm included 11% MSSA infections, for which vancomycin is substandard therapy. The other RCT evaluated the efficacy of 2 higher-dose weekly doses of dalbavancin for osteomyelitis, performed in Ukraine. This study showed high success rates for dalbavancin (97%) for gram-positive osteomyelitis, although methodological flaws preclude strong conclusions about efficacy versus the standard of care arm, which did not represent usual practice (vancomycin was used for MSSA, and levofloxacin IV monotherapy was used for MSSA).

Real-world applications of dalbavancin and oritavancin for non-SSTI indications describe over 200 patients treated for osteomyelitis, endocarditis, bacteremia, and prosthetic joint infections with high success rates overall, but without comparison groups and limited reporting on adverse effects.[59-64] It is unclear from these studies how many of these infections could have been treated using oral antibiotics.

Evidence for Long-Acting Intravenous Antibiotics Among People Who Inject Drugs

Since long acting lipoglycopeptides became available, there has been interest in applying these lineless antibiotics to PWID. A few retrospective cohorts have evaluated the efficacy of dalbavancin among vulnerable populations, primarily PWID. Among 32 PWID with severe *S aureus* infections treated by dalbavancin, 56% had a clinical response, 13% with clinical failure, but 31% were lost to follow up with unknown outcome.[65] Bork and colleagues[66] reported the outcome of 28 patients receiving dalbavancin for non-SSTI in Baltimore, Maryland, of whom 16 (57%) were PWID. The cohort was comprised of primarily orthopedic infections and endocarditis, with a reported cure rate of 71%, but no information on the subgroup comprised of PWID.[28] Another group in Colorado included 11 PWID with non-SSTIs, but outcomes in this subgroup were not clearly described.[67]

Applying Long-Acting Intravenous Antibiotic Data to People Who Inject Drugs

The use of long-acting (LA)-IV antibiotics among PWID have the potential to address a few important problems in the management of IDU-associated infections. Adherence to daily oral antibiotics can be difficult for PWID with ongoing drug use and unstable social circumstances. The use of LA-IV for these infections is particularly encouraging given the high osteomyelitis success rate with only 2 doses of dalbavancin.[68] Concerns regarding access to follow-up and ability to adhere to treatment plans are not significantly mitigated by the use of LA-IVs. In the cohort of PWID treated with dalbavancin for *S aureus* infections, only 53% completed the planned course of therapy.[65] Although studies have documented cost savings by allowing earlier hospital discharge with LA-IV antibiotics, the use of oral antibiotics is likely to be even more cost-effective, further weakening the rationale for LA-IV therapy.[59,67]

SURGICAL PROCEDURES FOR THE TREATMENT OF INJECTION DRUG USE-ASSOCIATED INFECTIONS

Evidence for Surgical Interventions for Severe Infections in the General Population

With the exception of 1 RCT, data for indications and timing of valve surgery for infectious endocarditis are limited to observational data and subject to survivor and selection bias.[69,70] A propensity score-matched meta-analysis of early valve surgery (≤20 days) versus conventional therapy (surgery >20 days) or no surgery found early valve surgery was associated with decreased all-cause mortality compared with conventional therapy (odds ratio 0.41 [95% CI 0.31–0.54]).[69] The only randomized control trial evaluating timing of valve surgery for infectious endocarditis included patients with native left-sided infectious endocarditis who had large vegetations (>10 mm) and no urgent indication for surgery.[70] Early surgery reduced in-hospital mortality and embolic events, but not 6-month all-cause mortality. Only 8 patients in this trial had *S aureus* endocarditis, and none were reported to be PWID.

Evidence for Surgical Interventions for Severe Infections Among People Who Inject Drugs

The data on surgical outcomes for infections among PWID are primarily retrospective studies of valve surgery for IDU endocarditis. Most found that postoperative mortality among those with IDU-endocarditis and non-IDU-endocarditis was similar in the short-term.[71-73] The outcomes following the acute postoperative period among PWID appear to be worse, with 1 institution reporting a tenfold increase in mortality in the 3- to 6-month period following surgery.[72] Long-term mortality among PWID with endocarditis is high. In a cohort with a mean age of 36 years, the 10-year survival was just 44%.[7] Most deaths following valve surgery are related to ongoing IDU, and the need for reoperation was associated with increased mortality.[74] Importantly, addiction treatment referral is strongly correlated with survival among PWID with infectious endocarditis (hazard ratio 0.29).[32]

Applying Surgical Intervention Data to People Who Inject Drugs

When considering surgical interventions for PWID with severe infections, it is important to consider that even in the best circumstances, addiction is a relapsing disease, and ongoing episodes of drug use are expected.[75] In some cases, prosthetic material can be feasibly avoided, such as in tricuspid valve endocarditis. In this case, survival following tricuspid valve repair and replacement was similar, but repair was associated with lower risk for recurrent infection and need for reoperation.[76] Additionally, PWID tend to be younger, and many prosthetic devices have a finite lifespan. Thus, prosthetic material should be avoided whenever feasible, but the desire to avoid surgery should never supersede the most effective course of action to cure a severe infection. It may be true that PWID have higher medium-term mortality after endocarditis valve surgery compared with those who do not use injection drugs; however, the important unanswered question is how those with IDU-associated endocarditis would have done without any surgery. There are conflicting retrospective data on whether valve surgery is a predictor of survival in IDU-associated endocarditis.[7,32]

Application of surgical literature to PWID is also limited by the scant data on the effect of MOUD and other addiction treatments on infection-related outcomes. Most retrospective studies of IDU-associated endocarditis surgery do not report information on SUD diagnoses or utilization of MOUD. Outcomes following implementation of MOUD for patients with IDU-associated infections are being researched actively. Early reports from a cohort of IDU-associated endocarditis patients in Massachusetts indicate reduced mortality among those who took at least 3 months of MOUD following diagnosis.[77] Even without clear data on infection outcomes, MOUD should be routinely offered to patients with OUD based on strong evidence of decreasing overall mortality, retention in addiction treatment, and improved quality of life.[78]

SUMMARY

Successful management of IDU-associated infectious diseases requires a deliberate and earnest assessment of the literature and application to each unique patient. Clinical data supporting noninferiority of less-invasive, expensive, and dangerous approaches to infectious diseases should not be used as a license to deliver lower quality care to PWID. Instead, these data should be scrutinized to evaluate applicability to PWID, considering their unique challenges, before being carefully applied in practice. Fig. 1 provides a framework for considerations and treatment decisions for patients hospitalized with IDU-associated infections. Infectious disease, SUD, and environmental domains each play a vital role in the development of an individualized successful treatment plan. Most importantly, any treatment plan must be in line with a patient's values and preferences. Future research should focus on increasing the inclusion of PWID into pragmatic clinical trials, improving assessment of SUD diagnoses and utilization of MOUD, and working on comparing interventions between PWID rather than comparing primarily with other patients.

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KEY POINTS

- Application of the existing infectious disease (ID) literature to people who inject drugs (PWID) must consider their unique medical, psychological, and social challenges.
- Outpatient parenteral antimicrobial therapy can be successful among select PWID with injection drug use-associated (IDU) infections, especially when the alternative is prolonged hospitalization for intravenous antibiotics.
- Data supporting the use of oral antibiotics for severe bacterial infections should be applied with caution to PWID, and close ID follow-up and consideration of barriers to adherence to oral antibiotics are required.
- Literature on surgical management of IDU-associated endocarditis suggests worse long-term outcomes compared with other causes of endocarditis, but there are no prospective data comparing medical versus surgical approaches for IDU-associated endocarditis and little information on the effect of addiction treatment.

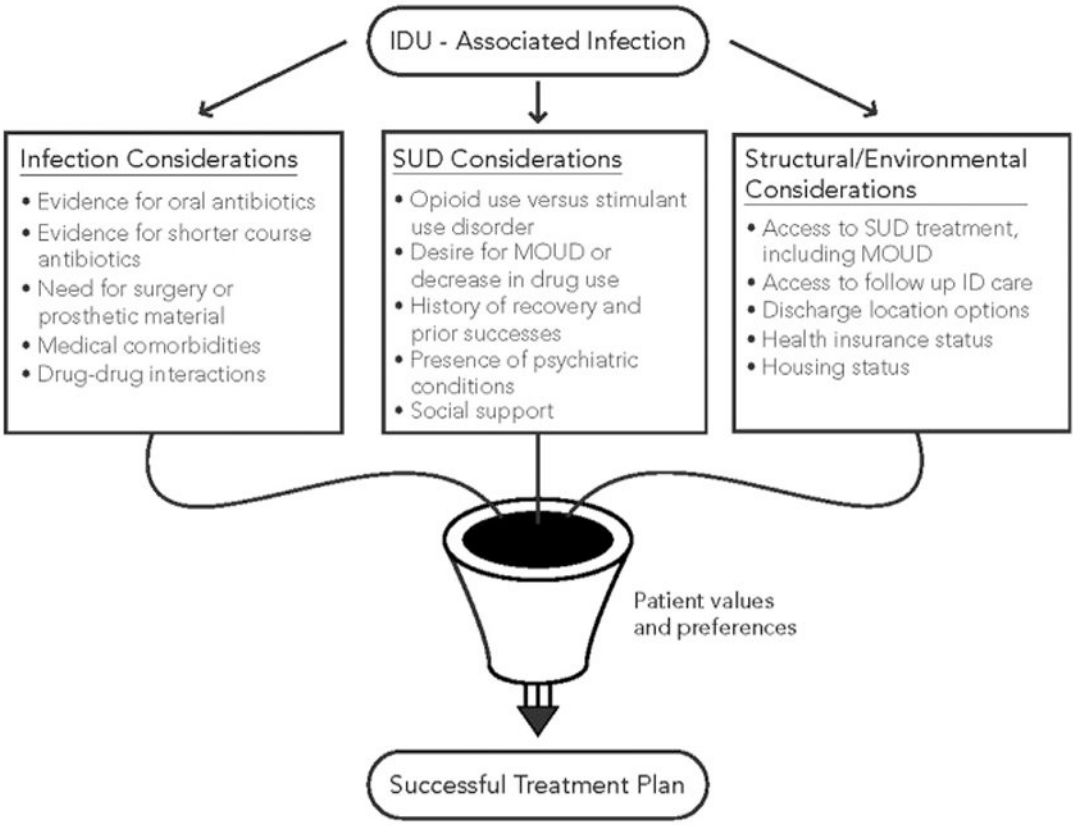

Fig. 1.

Factors to consider when developing an evidence-based treatment plan for IDU-associated infections. When confronted with an IDU-associated infection, clinicians must balance the best available ID literature (infection considerations) with a patient's SUD (SUD considerations). Both must be realistic and feasible given the local environment and social circumstances of the patient (structural/environmental considerations). Finally, any successful plan must be filtered through each individual's values and preferences.

Table 1

How people who Inject drugs differ from the general population represented In clinical trials for management of severe infections

Characteristics of People Who Inject Drugs	Implications for Injection Drug Use-Associated Infections
Younger age and fewer comorbidities • Median age of IDU-endocarditis patients almost half that of non-IDU-associated endocarditis (33 vs 63 y)[79]	• More physiologic reserve to survive severe infections than older multimorbid patients[80,81] • Less likely to experience life-threatening adverse events from antimicrobials[82,83] • May be able to tolerate longer courses of riskier antimicrobials (such as trimethoprim-sulfamethoxazole)
More mental health disorders • 29% with depression, 22% have attempted suicide, and symptoms of post-traumatic stress disorder are common[84] • Higher prevalence of substance-induced mood disorders, personality disorders, and anxiety disorders[85,86]	• Barriers to adhere to medical treatment plans • Drug interactions between psychoactive medications, illicit drugs, and antimicrobials
More chronic viral infections • Among PWID, global HIV prevalence is 18%, and in the United States it is 7%[87,88] • More than 50% of PWID are antibodypositive for HCV and 9% have chronic hepatitis B virus infection[88]	• Immunodeficiency of advanced HIV increases the chances of both opportunistic and typical infections, as does chronic liver disease from HCV or HBV • Drug interactions between antiretroviral therapy (ART) and antimicrobials often used for the treatment of severe infections
Stigmatization by health care system • Many report experiences of dehumanization and discrimination[89] • Experiences of trauma during prolonged hospitalization[28]	• Associated with delay in presenting for health care, self-treatment attempts, and seeking informal therapies from nonmedical personnel[90,91] • Untreated withdrawal and undertreated pain fuel behaviors like leaving the hospital AMA (or early discharge) and in-hospital illicit drug use[92,93] • Stigmatization of drug use may lead PWID to present with more advanced disease, creates barriers to completing care plans, and often results in early discharge without antimicrobials or follow-up[30]
More social barriers to care • 60% report past-year homelessness[94] • 74% uninsured, and 19% did not seek care from a medical provider within the last year[95]	• Difficulty adhering to medical treatment plans while homeless • Lack of access to follow-up medical care and difficulty paying for medications

Table 2

Common drug interactions between antimicrobials and medications for opioid use disorder

Antibiotic Class	Concern	Antibiotic	Medication for Opioid Use Disorder		
			Methadone	**Buprenorphine**	**XR-Naltrexone**
Fluoroquinolones	QTc prolongation – risk for adverse CV events increased with structural heart disease, electrolyte disorders, and likely by use of multiple QTc prolonging agents (eg,; SSRI)[96-100]	Moxifloxacin – highest QTc effect and strongest association with CV events among FQs[101] Levofloxacin – lower QTc effect and association with CV events compared with moxifloxacin[101] Ciprofloxacin – lower QTc effect and association with CV events compared with moxifloxacin and levofloxacin[101] Delafloxacin – industrysponsored studies suggest no QTc effect; limited postmarketing data[108,109]	Associated with QTc prolongation, but weak association with CV events Most cases reported to the FDA had other risk factors for QTc prolongation[102-104]	In vitro blockage of cardiac potassium voltage-gated channels, but no QTc prolongation in the absence of concomitant CYP inhibitors[105-107]	Not associated with QTc prolongation
Oxazolidinones	Serotonin toxicity – risk for serotonin toxicity increased by use of >1 serotonergic agent (eg, SSRI, MDMA, cocaine)	Linezolid – MAOI Most linezolid-associated serotonin toxicity cases reported were also on an SSRI[110] One case control study showed similar risk for serotonin toxicity when linezolid is used with or without an SSRI[111] Tedizolid – preclinical studies suggest less MAOI compared with linezolid and lower risk for serotonin toxicity Patients on SSRI excluded from clinical trials[116] Limited postmarketing data	Weak serotonin reuptake inhibitor One case report of serotonin toxicity associated with methadone and linezolid coadministration[112] Package insert recommends careful observation with slow incremental methadone doses if used together with an MAOI or ≤14 d of stopping a MAOI[113]	No serotonin reuptake inhibitor activity predicted in vitro[114] One published report of serotonin toxicity in patient taking tricyclic antidepressants Prescribing information does not recommend use together with an MAOI or ≤14 d of stopping a MAOI[115]	Not associated with serotonin toxicity
Rifamycins	CYP induction leading to increased metabolism of CYP substrates Induction can occur within hours of first dose Induction reversal can take up to 2 weeks after discontinuation	Rifampin – potent CYP3A inhibitor Rifabutin – less potent CYP3A inhibitor compared with rifampin Limited clinical data for bacterial infections compared with rifampin[120]	Methadone is a CYP substrate and rifampin-induced withdrawal is well described.[117] Rifabutin does not appear to precipitate methadone withdrawal. Rifamycin/methadone combination not contraindicated, but careful monitoring needed[118]	Buprenorphine is a CYP substrate, and rifampin coadministration can induce withdrawal Rifabutin decreases buprenorphine levels, but does not appear to precipitate withdrawal Buprenorphine decreases rifabutin levels, but clinical significance unclear[119] Rifamycin/ buprenorphine combination not contraindicated, but careful monitoring needed Consider rifabutin therapeutic drug monitoring	Not metabolized by CYPs No known interaction with rifamycins

Abbreviations: CV, cardiovascular; FQ, fluoroquinolone; MAOI, monoamine oxidase inhibitor; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); SSRI, selective serotonin reuptake inhibitor.

Table 3

Benefits and risks of implementing selected evidence-based practices for injection drug use-associated infections

	Benefits	Risks
OPAT vs extended hospitalization	• Completing treatment in more acceptable environment • Increased autonomy, ability to reintegrate, and enter recovery • Avoid traumatic aspects of extended hospitalization	• Nonadherence with potential for worsening infection • PICC-associated complications • Lack of close monitoring for toxicity and worsening infection • Exposure to drug use triggers
Oral vs intravenous antibiotics	• Helps avoid prolonged hospitalization • Increased autonomy, ability to reintegrate, and enter recovery • Lack of need for PICC • Allows most diverse discharge options	• Nonadherence with potential for worsening infection • Less clinical experience and data for PWID • Lack of close monitoring for toxicity and worsening infection • Exposure to drug use triggers • Requires close outpatient follow-up that may not be feasible • More drug-drug interactions
Shorter vs longer course antibiotics	• Less risk for antibiotic adverse events • Potential for shorter hospitalization and need for IV antibiotics	• Requires close outpatient follow up for response to treatment • Little clinical data specific to PWID
Long-acting IV vs standard oral or IV antibiotics	• IV bioavailability without the need to remain hospitalized • No need for PICC • Given long half-life, may be more tolerant of nonadherence	• High cost • Logistical difficulties of finding infusion chair • Only for gram-positive organisms
Surgery vs medical management	• Decreased complications/tissue destruction by infection (eg, shortened duration of sepsis, fewer debilitating emboli) • Potential for shorter course antibiotics, and shorter hospitalization	• Increased risk of reinfection, prosthetic device infection, especially in setting of ongoing drug use • Finite lifespan of many prosthetic devices