



REVIEW

Emerging Viral and Bacterial Infections: Within an Era of Opioid Epidemic

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ABSTRACT

The opioid epidemic is a public health crisis that continues to impact healthcare in the United States of America (USA). While changes in opioid prescribing have curbed the medical use of opioids, the increase in nonmedical use, largely driven by injection drug use (IDU), has contributed to the escalating incidence of opioid use disorder (OUD). Furthermore, IDU is associated with high-risk injection practices that can increase the risk of acquiring viral and bacterial infections. Here in this comprehensive review, we aimed to summarize the epidemiology and management of OUD, along with the screening and antimicrobial treatment of associated infections, specifically focused on human immunodeficiency virus, hepatitis C virus, skin and soft tissue infections, endocarditis, and osteomyelitis. Medication-assisted therapy (MAT) and infection guidelines from the USA will be presented.

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Key Summary Points

Opioid use disorder is a growing problem in the USA.

Opioid use disorder can lead to injection drug use and substance abuse.

Injection drug use is comorbid with viral infections such as hepatitis C and human immunodeficiency virus as well as bacterial infections.

Healthcare providers play a vital role in early detection of opioid use disorder and thus resources should be available to educate providers and patients.

DIGITAL FEATURES

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EPIDEMIOLOGY

The opioid epidemic is a growing problem that has increased mortality and hospitalization since its emergence. In 2017, the US Department of Health and Human Services (HHS) declared the opioid epidemic as a public health emergency. In 2018, the United Nations Office on Drugs and Crime (UNODC) launched a strategic response to combat the epidemic. The opioid epidemic began in the 1990s in the USA, marked by increased prescribing of opioids and methadone for the management of acute and chronic pain relief. Prescriptions for opioids increased significantly from 180 morphine milligram equivalents (MME) per capita in 1999 to a peak of 782 MME per capita in 2010 [1]. Prescribing rates stayed constant between 2010 and 2012, and then began to decline. In 2015, the USA rate of opioid prescribing decreased 20% to 640 MME per capita [2]. Despite the decline in opioid prescribing rates, the rate in 2015 was three times higher than the reported rate in 1999. The extensive medical prescribing of opioids from 1990 into the early 2000s led to widespread community use and dependence. As prescribing standards became more stringent and regulated, patients increasingly began to seek opioids from illegal sources. These unregulated sources of opioids are now a factor in the increasing death rate from opioid overdoses and are a major contributor to the opioid use disorder (OUD) we encounter today [3]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

OPIOID USE DISORDER

The opioid epidemic gave rise to the increasing incidence of OUD, which is a chronic lifelong disorder with potentially significant health consequences including disability, relapse, and death [4]. Opioids that have contributed to the emerging epidemic include prescription-based (i.e., fentanyl and oral pain relievers such as oxycodone and hydrocodone) and heroin. The American Psychiatric Association DSM-5 criteria

define OUD as a problematic pattern of opioid use, including tolerance, impaired occupation/social function, craving, or continued dependence despite worsening psychological distress or withdrawal, within a period of 12 months. Mechanistically, opioids activate the mu-opioid receptor to reduce the perception of pain but can also activate the mesolimbic (midbrain) reward system [5]. The reward system in the ventral tegmental area releases dopamine in the nucleus accumbens, eliciting feelings of pleasure and euphoria. As a result, chronic use of opioids leads to conditioned associations and positive reinforcement of this euphoric state, thus increasing the risk for OUD despite the potential for negative consequences [4, 5].

Despite the availability of effective opioid treatment programs, there are still many deaths related to opioid overdoses in the USA. In 2018, nearly 70% of 67,367 deaths due to drug overdoses involved an opioid [3]. On average, the overdose death rate increased by 10% per year from 1999 through 2006, by 2% per year from 2006 through 2013, and by 14% per year from 2013 through 2016 [6]. The age-adjusted rate of drug overdose deaths involving synthetic opioids such as fentanyl, fentanyl analogues, and tramadol, increased by 188% from 0.3 per 100,000 standard population in 1999 to 1.0 in 2013, and 9.9 in 2018 [6, 7].

Currently, the Centers for Disease Control and Prevention (CDC) attributes illicit synthetic opioids as the driver of drug overdose death in the USA [8–11]. In fact, fentanyl, first approved by the Food and Drug Administration (FDA) in 1998 to treat breakthrough cancer pain, is 50–100 times more potent than morphine and can be produced in illegal laboratories [12]. Illegally produced fentanyl is often cheaper and easier to obtain than heroin or prescription fentanyl. Illicit fentanyl can be used as an additive to heroin, cocaine, or other counterfeit pills, which makes uninformed users more susceptible to addiction and overdose [13].

As people with OUD shift from prescription opioids to cheaper street alternatives, the use of heroin has also increased within the USA. In 2010, approximately 600,000 people reporting

Table 1 Medication-assisted treatment (MAT) for opioid use disorder (OUD)

Medication	Mechanism of action	Dose and recommendations	Treatment considerations
Buprenorphine	Mixed agonist/antagonist: partial mu-opioid receptor agonist and kappa-opioid receptor antagonist	Individualize on the basis of patient's opioid use Usual dose range: 4–24 mg sublingually once or twice daily	Potential interactions with CYP inhibitors or inducers Available co-formulations with naloxone Must educate the patient on appropriate administration technique, especially for sublingual administration
Methadone	Agonist at the mu-opioid receptor and antagonist at the <i>N</i> -methyl-D-aspartate (NMDA) receptor	Individualize dose. Patients who receive higher doses (> 100 mg) are more likely to remain compliant with treatment	Potential interactions with CYP inhibitors or inducers QTc prolongation is a concern at higher doses Can only be prescribed for OUD by a licensed opioid treatment program
Naltrexone	Antagonist at opioid receptor	50–100 mg by mouth once daily Depot formulation: fixed-dose monthly injection	No significant interactions Longer time of continuous abstinence in those who received depot formulation compared to placebo after transition from prison to community

Adapted from treatment options for opioid use disorder within HIV guidelines [28]

heroin use compared with 400,000 people in 2002 [14]. The increase in heroin use has also contributed to the overall increase in overdose-related deaths, already reported with prescription opioids. In 2018, nearly 15,000 people died from a drug overdose involving heroin in the USA, a rate of almost five deaths for every 100,000 Americans [15]. Furthermore, the association of oral opioid misuse and injection heroin use is also escalating [16–18], as many individuals transition from oral opioids to injectable heroin due to its increased potency [16, 19, 20]. The increase of injection drug use (IDU) within the opioid epidemic drives a surge in both viral and bacterial infections, including human immunodeficiency virus (HIV)

infection, viral hepatitis, infective endocarditis, and skin and soft tissue infections [21, 22].

MEDICATION-ASSISTED THERAPY (MAT)

MAT is a major component of OUD treatment programs. Treatment options for MAT are provided in Table 1. All three medications target the central mu-opioid receptor for therapeutic activity; however, they differ slightly in their pharmacokinetic and pharmacodynamic properties. All three medications are useful in treating the physiological dependence associated with OUD; however, the addition of an opioid antagonist in maintenance therapy doubles

Table 2 Epidemiology, risk factors, and antimicrobial treatment of infections associated with injection drug use

Infection type	Epidemic (1990s–2015)	Current (2016–Present)	Risk factors	Antimicrobial treatment
HIV [28–31]	2016: Estimated 1.1 million people aged 13 and older had HIV in the USA, including an estimated 162,500 (14%) people whose infections had not been diagnosed		Residential instability Risky sexual behavior (unprotected sex, multiple partners, exchanging sex for drugs or money) Needle sharing Caucasian Recent cocaine use Women: binge drinking, poorer mental health	Recommended initial regimens for persons with HIV Bictegravir/tenofovir alafenamide/emtricitabine Dolutegravir/abacavir/lamivudine—only for individuals who are HLA-Bb5701 negative and without chronic hepatitis B virus (HBV) co-infection Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate) Dolutegravir/lamivudine—except for individuals with HIV RNA > 500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available Raltegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate) For a complete list of therapies, refer to HIV guidelines [28]
Hepatitis C [32–36]	2011: 16,500 2013–2016: 2.4 million persons who were HCV RNA positive (1% prevalence among adults) 2016: 41,200		Risky sexual behavior (unprotected sex, multiple partners, exchanging sex for drugs or money) Recent IDU Recent cocaine use Older age Hispanic	Direct-acting antivirals Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir Sofosbuvir/velpatasvir Dependent on genotype; refer to HCV guidelines for complete list of therapies and duration

Table 2 continued

Infection type	Epidemic (1990s–2015)	Current (2016–Present)	Risk factors	Antimicrobial treatment
Skin and soft tissue infection (SSTI) [37, 38]	N/A		Trauma/injury Diabetes (peripheral artery disease, neuropathy) IDU Prolonged hospitalization Sports teams Dialysis	Antibiotics (see Table 8 for detailed regimens)
Infective endocarditis [39, 40]	2002: 8% in USA 2016: 16.3% in USA		IDU Prosthetic heart valves Congenital heart defects	Antibiotics, antifungals (see Table 9 for detailed regimens)
Osteomyelitis [41–43]	N/A		IDU Diabetes (peripheral artery disease, neuropathy) Long-term SSTI Prosthetic joints Smoking (poor circulation) Sickle cell disease Cancer	Antibiotics (see Sect. “Osteomyelitis” and refer to IDSA guidelines [43])

opioid abstinence success rate compared to treatments without opioid antagonists [23]. The use of oral naltrexone without combination opioid agonist is FDA approved to treat OUD; however, it is often excluded from consideration because of poor adherence and poor outcomes in clinical studies [24]. In addition to pharmacologic support, OUD treatment programs use social support and counseling to help decrease opioid cravings.

Outcomes for MAT in among persons who inject drugs (PWID) are promising. Of PWID diagnosed with HIV and concomitantly on MAT, there was a 69% increase in recruitment onto antiretroviral therapy (ART), 54% increase in ART coverage, a twofold increase in adherence, and 23% decrease in the odds of attrition compared to those not on MAT [25]. Other

harm reduction strategies include overdose education, safe injections spaces and sterile needle programs. Syringe service programs provide IDUs with sterile syringes and other equipment to reduce the risk of HIV and hepatitis C virus (HCV) transmission. A prospective study in New York City found that HIV prevalence declined from 80% to 59% and HCV rates declined from 90% to 63% from 1990 to 2001 in PWID. These corresponded to an increase in the number of syringes distributed by these programs, ranging from 250,000 to 3,000,000 syringes exchanged annually [26]. In addition, MAT has been proven to improve social outcomes for parents with OUD with lower incidence of child mistreatment and introduction into the foster-care system [27] (Table 2).

VIRAL INFECTIONS

The augmented use of IDU within the opioid epidemic has led to an increase in viral infections, such as HIV and hepatitis C virus (HCV). HIV and HCV infections are transmitted between individuals through high-risk injection practices, such as sharing syringes, drug paraphernalia, and high dead-space syringes [44]. Another mode of transmission is unprotected sex, in which one study reported its increase in individuals using non-medical prescription opioids [45]. The management of HIV and HCV infections in PWID should focus on treatment, continual monitoring, adherence, and harm reduction. The sections that follow address the management of these viral infections.

Human Immunodeficiency Virus

In 2016, injection opioid use was responsible for 13% of new HIV diagnoses and linked to localized outbreaks in Scott County, Indiana and Lawrence and Lowell, Massachusetts [44]. PWID accounted for 9% (3641/38,739) of new HIV diagnoses in the USA in 2017 [46]. Although other factors, such as ART coverage, have increased from 58% to 71% between 2009 and 2015 among people with HIV who also engaged in IDU [47], patients still face social and economic barriers that limit access to HIV prevention and treatment services. One study found that more than half (56%) of PWID reported being homeless, 25% reported being incarcerated, and 16% reported having no health insurance in the preceding 12 months [46].

The US HHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV do not have a specific section dedicated to PWID, but recognize the presence of substance use disorders (SUD) among people with HIV [28]. Unaddressed SUD may prevent an individual from being tested for HIV, initiating ART, or adhering to ART. Furthermore, unaddressed SUD can increase behaviors that place a person at risk for HIV transmission; therefore, it is critical to address SUD to mitigate potential barriers to treatment [28]. Key considerations and recommendations for managing

HIV patients with SUD are summarized in Table 3. Generally, ART regimens should be simplified to maximize adherence. If possible, patients should receive once-daily, single-tablet regimens with a high barrier to developing resistance and a low risk of hepatotoxicity [48].

Ideal ART regimens combine high efficacy, high tolerability, low toxicity, low pill burden, affordability and availability. The HIV guidelines list the following regimens as recommended initial regimens for most people with HIV:

- Bictegravir/tenofovir alafenamide/emtricitabine
- Dolutegravir/abacavir/lamivudine—only for individuals who are HLA-Bb5701 negative and without chronic hepatitis B virus (HBV) co-infection
- Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)
- Dolutegravir/lamivudine—except for individuals with HIV RNA > 500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- Raltegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)

Table 4 lists potential ART regimens with respect to patient-specific factors and clinical scenario considerations.

In patients with SUD, the HIV guidelines recommend evidence-based pharmacotherapy according to specific substance use disorder, including alcohol and nicotine (Table 5). Alcohol consumption in HIV is estimated to be greater than 50%, with a range of 54–67% [49, 50]. Unhealthy alcohol use can increase the frequency of risky behaviors associated with sexual transmission of HIV and has been linked to HIV acquisition [28]. In addition, unhealthy alcohol use has also been associated with lower adherence to ART [28]. Ongoing alcohol use is not a contraindication to receive ART; however, addressing alcohol use may improve treatment outcomes [51]. FDA-approved pharmacotherapies can also be prescribed for alcohol use disorder (Table 5).

Table 3 Key considerations and recommendations for patients with SUD disorders and HIV [28]

Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care
Healthcare providers should be nonjudgmental when addressing substance use with their patients
Persons with HIV and SUDs should be screened for additional mental health disorders
Persons with HIV and SUDs should be offered evidenced-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment) as part of comprehensive HIV care in HIV clinical settings
Ongoing substance use is not a contraindication to antiretroviral therapy (ART). Persons who use substances can achieve and maintain viral suppression with ART
Substance use may increase the likelihood of risk-taking behaviors (e.g., risky sexual behaviors), the potential for drug–drug interactions, and the risk or severity of substance-associated toxicities (e.g., increased hepatotoxicity or an increased risk of overdose)
Selection of ART regimens for individuals who practice unhealthy substance and alcohol use should take potential adherence barriers, comorbidities which could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug–drug interactions, and possible adverse events associated with the medications into account
ART regimens containing once-daily dosing of single-tablet regimens with high barriers to resistance, low potential for hepatotoxicity, and low potential for drug–drug interactions are preferred

The prevalence of tobacco smoking among persons with HIV in the USA is approximately 33.6% versus 16.8% in the general population [28]. Among 17,995 HIV-infected individuals on ART in Europe and North America, individuals who smoked had nearly twice the mortality of

those who did not (mortality rate ratio 1.94; 95% CI 1.56–2.41), with significant mortality attributed to cardiovascular disease and non-AIDS-related malignancy at increasing age [52]. Therefore, cessation of tobacco can lead to improved quality of life in these individuals. Clinicians should consider using behavioral and pharmacological approaches when treating patients with HIV who use tobacco. These include, but are not limited to, advising the patient to quit smoking, using the five A's (Ask, Advise, Assess, Assist, and Arrange), motivational interviewing, and referring the patient to a tobacco quitline [28]. Pharmacotherapies for smoking cessation are described in Table 5.

The guidelines emphasize that while treatment for an OUD can improve HIV treatment outcomes, it is not a prerequisite for treating HIV. Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people with IDU were less likely to be retained in care [53]. In addition, people with IDU and non-injection drug users (non-IDU) had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort. In 2001, 68.4% of PWID were retained in care, 45.5% on ART, and 28.0% virally suppressed, compared to 79.4%, 62.4%, and 41.7% of non-IDU, respectively. However, these gaps closed by 2010. In 2012, 82.2% of PWID were retained in care, 76.3% on ART, and 69.1% virally suppressed, compared to 80.9%, 77.1%, and 71.0% of non-IDU, respectively, demonstrating that patients are able to successfully adhere to ART despite ongoing opioid use [53].

The closed gap can be attributed to multiple interventions as previously referenced including MAT, syringe service programs, and overdose education and naloxone distribution. For PWID, sharing needles and syringes is a major route of transmission for HIV, and needle and syringe programs (NSPs) are considered a key component of management of PWID [54]. NSPs are community-based programs that provide access to sterile needles and syringes, facilitate safe disposal of used syringes, and provide or link to other services such as MAT and naloxone distribution and education [55]. A meta-analysis of 13 systematic reviews found that NSPs were

Table 4 Recommended ART regimens based on selected patient-specific factors and clinical scenarios [28]

Clinical scenario	Medication	Dose
Single-tablet regimen options for initial therapy	BIC/TAF/ FTC	1 tablet once daily
	DOR/TDF/ 3TC	1 tablet once daily
	DRV/c/TAF/ FTC	1 tablet once daily with food
	DTG/ABC/ 3TC	1 tablet once daily
	DTG/3TC	1 tablet once daily
	EFV/TDF/ FTC	1 tablet once daily on an empty stomach, preferably at bedtime
	EVG/c/TAF/ FTC	1 tablet once daily with food
	EVG/c/TDF/ FTC	1 tablet once daily with food
	RPV/TAF/ FTC	1 tablet once daily with a meal
	RPV/TDF/ FTC	1 tablet once daily
	High barrier to resistance	BIC DTG
Potential for hepatotoxicity	DTG ZDV RPV DRV MVC	
Drug–drug interactions	Least: integrase inhibitors (BIC, DTG, RAL) Most: pharmacokinetic boosters (COBI, RTV)	
On medication-assisted treatment for opioid use disorder	Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring recommended	

3TC lamivudine, ABC abacavir, BIC bictegravir, COBI cobicistat, DOR doravirine, DRV darunavir, DRV/c darunavir/cobicistat, DTG dolutegravir, EFV efavirenz, EVG elvitegravir, EVG/c elvitegravir/cobicistat, FTC emtricitabine, MVC maraviroc, RAL raltegravir, RPV rilpivirine, RTV ritonavir, TAF tenofovir alafenamide, TDF tenofovir disoproxil fumarate, ZDV zidovudine

Table 5 Medications for treatment of substance use disorders [28]

Medication	Dose and recommendations	Potential interactions with ART	Comments
Alcohol use disorder			
Acamprosate	666 mg PO three times a day Or 333 mg PO three times a day for patients with creatinine clearance (CrCl) 30–50 mL/min	No significant interaction with ART drugs expected	Contraindicated in patients with CrCl < 30 mL/min
Disulfiram	250 mg PO once daily	Use with caution when prescribing an ART oral solution that contains ethanol and/or propylene glycol (e.g., fosamprenavir, lopinavir/ritonavir, ritonavir)	Counsel patients regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension
Naltrexone	50–100 mg PO once daily depot formulation is a fixed-dose monthly injection	No significant interaction with ART drugs expected	Has the greatest efficacy of all FDA-approved medications for alcohol use disorder
Nicotine use disorder			
Nicotine replacement therapy	There are a wide variety of FDA-approved nicotine replacement products. All formulations are effective	No significant interaction with ART drugs expected	Work with the patient to identify the route of delivery that the patient will use and find most helpful
Bupropion	Start at 150 mg PO daily for 3 days, then increase to either 150 mg twice daily or 300 mg once daily (only use formulations that are approved for once-daily dosing)	Concentration may be reduced when used with ART drugs that are CYP2D6 inducers. Refer to guidelines for further recommendations	Tobacco quit date should ideally be 1 week after starting therapy
Varenicline	Titrate dose on basis of tolerability until desired effect is achieved. The goal is to reach a dose of 1 mg PO twice daily Requires dose adjustment in patients with CrCl < 30 mL/min	No significant interaction with ART drugs expected	Tobacco quit date should ideally be 1 week after starting therapy

Table 6 Recommendations for screening and management of HCV infection in people with IDU [36]

Annual HCV testing is recommended for PWID with no prior testing, or past negative testing with subsequent IDU. Depending on the level of risk, more frequent testing may be indicated
Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV antibody testing with reflexive or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected
PWID should be counseled about measures to reduce the risk of HCV transmission to others
PWID should be offered harm reduction services, including intranasally administered naloxone, needle/syringe service programs, medications for OUD, and other SUD treatment programs
Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment
At least annual HCV-RNA testing is recommended for PWID with recent IDU after they have spontaneously cleared HCV infection or have been successfully treated

effective in reducing HIV transmission among PWID [54]. Multiple studies have shown that effective NSPs significantly reduce the prevalence of HIV and person-years at risk for HIV in PWID [56, 57].

Hepatitis C Virus

The number of newly reported HCV diagnoses nearly tripled from 2010 to 2015, with the highest overall number of new infections among those in their twenties largely resulting from IDU [58]. Hepatitis C poses an immense threat to PWID as approximately 50% of PWID are HCV-antibody positive [59]. According to the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) guidelines, the first few years after an individual begins to inject drugs

are a high-risk period during which the incidence of contracting HCV can exceed 40% [36]. In fact, the CDC reported that 64% of acute HCV infections were in PWID in 2015 [32]. In the absence of a vaccine, the AASLD/IDSA guidelines recommend HCV screening combined with antiviral treatment and other care services (e.g., SUD treatment and needle exchange program) as a potential strategy to decrease the incidence of HCV infection [36]. Recommendations by AASLD/IDSA for the screening and treatment of HCV infection in PWID are summarized in Table 6. In general, all individuals who currently or previously engaged in IDU should be tested for HCV infection. If an HCV antibody test is positive, it should be confirmed by HCV-RNA testing.

There are seven HCV genotypes, of which genotype 1 is the most common in the USA. However, one study found that HCV genotypes 3 and 4 were more significantly prevalent among HIV/HCV co-infected patients in Serbia [60]. Current direct-acting antiviral (DAA) treatment recommendations from the AASLD/IDSA for treatment-naïve genotype 1 and 3 HCV infections are simplified in Table 7.

Concerns exist among healthcare providers that PWID may fail treatment because of non-adherence and dropout in real-world settings. However, a recent study in the USA found that overall rates of sustained virologic response (SVR) were similar between patients who were active drug users or receiving MAT (96% of 46) versus those who were not (95% of 43) [61]. To improve adherence, the PREVAIL study evaluated three models of HCV treatment, comparing 150 patients on MAT with directly observed treatment, group medical visit treatment in which subjects attended weekly treatment, and treatment as usual, in which patients took their own medication [62]. The study suggested that patients in the directly observed and group treatment arms achieved a higher SVR at 12 weeks than in the treatment as usual. SVRs for directly observed treatment, group medical visit, and treatment as usual were 98%, 93%, and 89%, although this was not statistically significant ($p = 0.19$) [62].

Table 7 Antiviral treatment recommendations for HCV infection by genotype [36]

Genotype	Cirrhosis	Agent ^a	Duration (weeks)
1a	With or without compensated cirrhosis	Elbasvir/grazoprevir ^b	12
		Glecaprevir/pibrentasvir ^b	8
		Ledipasvir/sofosbuvir ^b	12
		Sofosbuvir/velpatasvir ^b	12
	Without cirrhosis	Ledipasvir/sofosbuvir if HIV-uninfected and HCV RNA < 6 million IU/mL ^b	8
1b	With or without compensated cirrhosis	Elbasvir/grazoprevir ^b	12
		Glecaprevir/pibrentasvir ^b	8
		Ledipasvir/sofosbuvir ^b	12
		Sofosbuvir/velpatasvir ^b	12
	Without cirrhosis	Ledipasvir/sofosbuvir if HIV-uninfected and HCV RNA < 6 million IU/mL ^b	8
3	Without cirrhosis	Glecaprevir/pibrentasvir ^b	8
	Compensated cirrhosis	Glecaprevir/pibrentasvir ^b	12
	With or without compensated cirrhosis without Y93H mutation	Sofosbuvir/velpatasvir ^b	12
	With compensated cirrhosis and Y93H mutation	Sofosbuvir/velpatasvir/voxilaprevir	12
	No cirrhosis	Daclatasvir + sofosbuvir	12
	Compensated cirrhosis	Daclatasvir + sofosbuvir ± ribavirin	24

^a All are single-tablet regimens dosed once daily

^b Denotes preferred regimen

BACTERIAL INFECTIONS

Like viral infections, bacterial infections can also be easily transmitted and acquired through IDU. The CDC and HHS reported that IDUs are 16.3 times more likely to develop invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections than non-IDU [63]. Among the IDU population, MRSA infections have increased from 4.1% in 2011 to 9.2% in 2016 [63]. Risk factors that increase the likelihood of spreading and acquiring bacterial infections are similar to viral infections and include contamination of injectable drugs, drug injection paraphernalia, reuse of needles for injection,

and non-sterile injection sites. Common bacterial infections in this population consist of local (e.g., cellulitis or skin abscesses) and systemic infections (e.g., infective endocarditis or osteomyelitis) [63].

Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTIs) are common in the IDU population as a result of the nature of injection that disrupts the dermis and thus SSTIs are the most common cause of hospital admission for PWID [64]. This is not surprising, given that an important risk factor is the disruption of the skin, which is the major

Table 8 Antimicrobial therapy for skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus* [38]

Antimicrobial	Dose	Comment
Vancomycin	Target trough concentrations of 10–15 mg/L ^a	Parenteral drug of choice for MRSA infections; alternative for penicillin allergic patients
Linezolid	600 mg IV BID OR 600 mg PO BID	
Clindamycin	600 mg IV TID OR 300–450 mg PO QID	Inducible resistance in MRSA
Daptomycin	4 mg/kg IV q24h	Monitor creatinine phosphokinase (CPK), possible myopathy
Doxycycline ^b	100 mg PO BID	Not recommended for age < 8 years
Ceftaroline	600 mg IV BID	
Trimethoprim–sulfamethoxazole ^b	1–2 double strength (160/800 mg) tablets PO BID	

^a Current national guidelines recommend dosing and monitoring by area under the curve rather than trough concentrations, but exclude non-invasive infections like SSTI

^b Requires additional streptococcal coverage

organ protecting humans from infections. A multivariate analysis identified that the disruption of the cutaneous skin barrier is one of the biggest risk factors for developing cellulitis [65]. However, an accurate assessment of the incidence is challenging given variable presentations and unreporting of SSTIs. Regardless, the incidence of clinically diagnosed SSTIs was estimated at 500 per 10,000 persons per year [66]. A high prevalence of cellulitis and skin abscesses among IDUs was reported in San Francisco in 1997. Notably, 85% of these 169 IDUs injected heroin, a commonly abused drug contributing to OUD. Other drugs that were abused by these IDUs were methamphetamine and cocaine. Approximately 32% of IDUs developed an active SSTI (i.e., abscess, cellulitis, or both) and 19 of these IDUs had multiple abscesses. Additionally, 68% of recruited IDUs reported a past infection consisting of an abscess, and 48% of these IDUs reported never seeking medical treatment for their abscess. The likelihood of developing cellulitis or abscess did not significantly differ between IDUs of different living statuses (e.g., homelessness), the type

of drug injected, or the location of injection [67].

Similarly, a study conducted in Denver also reported a high rate of skin infections (including abscesses) among IDUs. The most common drug of abuse was heroin, reported in 41% of 51 IDUs. In addition, 55% of these recruited subjects reported a previous bacterial skin infection directly related to injecting drugs, with an average of 4–6 bacterial skin infections per lifetime. Furthermore, 29% of IDUs reported an active abscess or abscess within the past year [68]. Lastly, in 2009, 28% of IDUs in the UK reported an injection-site infection with complications that ranged from uncomplicated cellulitis and local abscesses to necrotizing fasciitis and severe sepsis [69].

The most common pathogens causing cellulitis are beta-hemolytic streptococci. Within this subset of streptococci, *Streptococcus pyogenes* (group A *Streptococcus*) is the most common species [70–72]. For skin abscesses, the most common offending pathogen is *Staphylococcus aureus*, regardless of IDU [73]. These pathogens include both methicillin-susceptible and

Table 9 Antimicrobial therapy for infective endocarditis [40]

Antimicrobial	Dose	Duration (weeks)	Comments
Right-sided native valve endocarditis			
MSSA			
Nafcillin or oxacillin	12 g/24 h IV divided into 4–6 equal doses	2	For complicated right-sided IE and for left-sided IE, treatment duration is 6 weeks
Cefazolin	2 g IV q8h	6	Avoid in beta-lactam allergy
MRSA			
Vancomycin	Target trough concentrations of 15–20 mg/L	6	Alternative if patient has severe beta-lactam allergy
Daptomycin	≥ 8 mg/kg IV q24h	6	Bactericidal, monitor CPK
Right-sided prosthetic valve endocarditis			
MSSA			
Nafcillin or oxacillin	12 g/24 h IV divided into 4–6 equal doses	≥ 6	Vancomycin should be used alternatively in patients with severe beta-lactam allergy; cefazolin may be substituted in patients with non-immediate-type hypersensitivity reactions to penicillin
Plus Rifampin	900 mg IV q24h or 300 mg PO q8h	≥ 6	
Plus Gentamicin	3 mg/kg IV q24h or 1 mg/kg IV q8h	2	
MRSA			
Vancomycin	Target trough concentrations of 15–20 mg/L	≥ 6	
Plus Rifampin	900 mg IV q24h or 300 mg PO q8h	≥ 6	
Plus Gentamicin	3 mg/kg IV q24h or 1 mg/kg IV q8h	2	

^a Current national guidelines recommend dosing and monitoring by area under the curve rather than trough concentrations; however, data to firmly recommend for the treatment of infective endocarditis are limited. Refer to complete guidelines for more information

methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively). While IDU is a risk factor for MRSA SSTIs, occurrences of MRSA SSTIs have also become common in individuals without established risk factors in various parts of the USA [74]. For the treatment of cellulitis in

IDU patients, the Infectious Diseases Society of America (IDSA) Practice Guidelines for SSTIs recommend the use of an antibiotic that is effective against both MRSA and streptococci. In cases of systemic infection, the use of intravenous antibiotics is warranted. The duration of

therapy is generally 7 days, but can vary depending on clinical response. Recommended treatment regimens for MRSA are listed in Table 8. For skin abscesses, the IDSA Practice Guidelines for SSTIs recommend incision and drainage as the primary management strategy. The addition of an antibiotic with MRSA coverage should only be an adjunct therapy to incision and drainage if the patient exhibits signs or symptoms of a systemic inflammatory response (temperature $> 38\text{ }^{\circ}\text{C}$ or $< 36\text{ }^{\circ}\text{C}$, respiratory rate > 24 breaths per minute, heart rate > 90 beats per minute, or white blood cell count $> 12,000$ or < 4000 cells/ μL) [38].

Infective Endocarditis

The incidence of infective endocarditis (IE) in IDUs has increased over the past few years, especially among the younger population. According to the CDC's Multiple Cause-of-Death database, nationwide hospital admissions due to IE for patients younger than 30 years old who are IDU increased from 11% in 2008 to 27% in 2014 [75]. Between 1996 and 2016, there were 55,212 deaths from IE associated with drug abuse (DA). The proportion of drug abuse-associated IE (DA-IE) deaths increased from 9.4% in 1999 to 18.9% in 2016 [76]. The proportion of deaths from DA-IE among patients younger than 35 years old exceeded the national average, as DA-IE deaths in this population increased from 12.4% in 1999 to 37.4% in 2016 [76]. These results were supported by another study showing the doubling of DA-IE in the USA from 8% in 2002 to 16.3% in 2016, with younger patients more frequently having comorbidities such as HIV, HCV, concomitant alcohol abuse, and liver disease. Rural areas, particularly in the Midwest, seem to carry an increased risk for rates of DA-IE [39]. Additionally, hospitalizations due to DA-IE in North Carolina increased significantly from 14% in 2009 to 56% in 2014. While there was no difference in mortality, DA-IE hospital lengths of stay were longer in IDUs than non-IDUs (26 days vs 12 days) [77].

IDUs are at highest risk of developing right-sided IE, as approximately 90% of right-sided IE

patients are IDUs [78]. The most common pathogen causing right-sided IE is *S. aureus* (including MRSA), which accounts for about 70% of cases and then followed by streptococci and enterococci [79]. Uncommon pathogens that cause right-sided IE are fungi and Gram-negative bacilli (including *Pseudomonas aeruginosa*) [80, 81]. Recommended treatment by the American Heart Association (AHA) guidelines for native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE) caused by *S. aureus* are outlined in Table 9 [40]. While the addition of gentamicin has traditionally been a part of standard therapy for right-sided IE, there is emerging evidence suggesting that it may not be necessary for uncomplicated right-sided IE. Specifically, the addition of gentamicin to cloxacillin 2-week therapy did not provide any therapeutic advantage; cloxacillin monotherapy was as effective as combination therapy [82]. Furthermore, the addition of gentamicin in patients with native valve endocarditis caused by *S. aureus* was associated with nephrotoxicity [83].

Osteomyelitis

Osteomyelitis is a bone infection that results from hematogenous or contiguous bacterial seeding into the bone. The most common bacteria responsible for osteomyelitis are *S. aureus* [84]. Osteomyelitis has multiple risk factors, including IDU. Like DA-IE, osteomyelitis in IDU occurs more often in younger individuals. One study conducted in West Florida retrospectively evaluated 2150 individuals with osteomyelitis and reported that those with opioid drug abuse were significantly younger by an average of 11.5 years and had significantly longer hospitalizations by an average 5 days longer than those with diabetes. This may be partly due to lack of central catheter lines among IDUs in the outpatient setting, which would require these individuals to stay in the hospital longer. Diabetic patients may also require amputations depending on comorbidities (such as peripheral artery disease), which may contribute to shorter hospitalizations as well. However, regardless of the rationale, osteomyelitis among IDUs has

been associated with younger age and shown to increase healthcare costs when compared to individuals with other common risk factors [85].

Although IDU is a well-documented risk factor for osteomyelitis, there is limited information on treatment recommendation for IDU-related osteomyelitis. When empiric therapy is warranted for suspected osteomyelitis, regimens should provide coverage for MRSA, streptococci, and Gram-negative bacilli. The IDSA Clinical Practice Guideline for Native Vertebral Osteomyelitis recommends an initial regimen of vancomycin (target trough concentration 15–20 mg/L) plus a 3rd or 4th generation cephalosporin. In the case of allergy or intolerance, alternative therapies may include a combination of daptomycin or fluoroquinolone. However, in patients with normal neurologic function and stable hemodynamics, it is recommended to hold antibiotic therapy until a pathogen is isolated for directed antimicrobial therapy [43].

CONCLUSION

All healthcare providers play a vital role in identifying substance abuse and OUD. Early identification is critical as the implications of long-term opioid and substance abuse are serious, potentially life-threatening. The implications include a myriad of other health complications, such as viral infections, bacterial infections, overdose, and death. Guidelines from HHS HIV/AIDS also endorse focusing on early signs of OUD and the use of MAT to prevent the spread of infection and reduce the risks of morbidity and mortality that are associated with opioid use.

For the infectious diseases community, provider training for early detection of OUD and antimicrobial stewardship can increase awareness in the community and provide PWID adequate social support and harm reduction resources. As infectious diseases providers are often a point of contact for patients hospitalized for these infections, they play a unique role by screening for OUD, initiating MAT, and facilitating linkage to ID and OUD management

after hospital discharge [86]. As such, obtaining a thorough history and background on patients to recognize the potential of opioid use as the underlying cause is a simple yet important step in combating the opioid epidemic. In addition, community resources such as expansion of clean sterile needles, safe injection spaces, and OUD education are critical to inform community members to prevent the spread of associated infections. As healthcare providers, future research is needed to identify neurochemical and psychosocial factors leading to OUD as well as reinforcement of antimicrobial stewardship and education on antibiotic resistance in the setting of IDU.

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