Chapter

Injection Drug Use-Associated Infective Endocarditis

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Abstract

Injection drug use-associated presents is a unique entity. The demographics of those affected and the clinical presentation are markedly different from those with endocarditis due to other causes. This group presents with a high proportion of right sided valve involvement, distinct pathophysiology, and a more varied array of infectious causes. The best management of these patients regarding medications and surgery remain hotly contested. The increased use of oral antibiotics and novel treatment techniques may expand safe and effective treatment for this group of patients.

Keywords: endocarditis, epidemiology, persons who inject drugs

1. Introduction

Injection drug use (IDU) has long been recognized as a risk factor for endocarditis with case reports of endocarditis in persons who inject drugs (PWID) dating back at least to the 1930s [1]. Injection drug use-associated infected endocarditis (IDU-IE) presents with a relatively unique clinical presentation, is associated with a wide variety of antimicrobial pathogens, and presents multiple practical and ethical challenges to providing effective treatment. We review in this chapter the epidemiology of IDU and resulting IDU-IE in various aspects of the globe. We then further assess the pathophysiology, clinical presentation, microbiology, and management strategies for effective IDU-IE treatment. We end with a brief review of novel approaches to treatment including treatment of the underlying substance use disorder.

2. Injection drug use and IDU-IE across the globe

The epidemiology of IDU-IE generally reflects that of all PWID in a given time and place. It is notoriously difficult to determine the prevalence of IDU in a given population due to the hidden nature of drug use. Measures are most limited outside of Europe, Asia, North America and Australia. With these limitations noted, it is estimated that 11 million persons injected drugs worldwide in 2019 [2]. Central Asia has higher rates of PWID than other parts of Asia but it is less populous than other parts of the Asian Continent. Therefore more than a quarter of all PWID are estimated to reside in East and Southeast Asia, at least 3–5 million persons [3]. A high rate of HIV co-infection in PWID in Asia has resulted in overlapping syndemics. The proportion

of females is highly variable with estimates ranging from only 3% in South Asia to 20.8% in East and Southeast Asia [3].

Europe has seen a progressive decline in IDU throughout the 2010s [4]. There is a wide range of prevalence of PWID in Europe with the lowest rates estimated in the countries of Belgium, Greece, Spain, Hungary, and the Netherlands. Eastern Europe has a larger proportion of PWID than Western Europe. Heroin is the predominant drug injected though stimulants and other medications are occasionally injected as well. Czechia reports a particularly high rate of methamphetamine-associated injection drug use compared to other European countries. An estimated 25–28% of PWID are women in Europe which is slightly lower than North America and Australia at 30 and 33% respectively [3, 5, 6].

The United States has seen a dramatic rise in IDU as part of an ongoing opioid epidemic. The FDA began fast-tracking opioid drug applications in the early 1990s and the Pain As a 5th Vital Sign™ campaign requiring frequent assessment, scaling and treatment of pain launched in 1995 [7, 8]. In 1996 the juggernaut Oxycontin® was unleashed by Purdue Pharma [9] with employed physicians to spread the message of 'safe yet effective' pain relief to other physicians by citing the 1% addiction rate from an out of context, single paragraph NEJM letter [10]. It gave away millions of coupons for free samples, and netted itself 1 billion in sales annually by 2001 [9, 11]. Opioid use increased 1448% from 1996 to 2011 [12] and in 2012 the CDC declared prescription opioid overdose a national epidemic [13] with reported increases in hepatitis C, hepatitis B, and IDU-IE shortly following. Substance use disorders proceeded to rise in populations who were disproportionately prescribed prescription opioids including rural populations [14] and women [15]. By the 2010s women had gone from approximately 20% of regular opioid users to 50% [16]. The opioid epidemic in the US has since shifted from the original prescription opioid predominance to heroin, synthetic fentanyl analogs, and co-administration of stimulants. These shifts have resulted in large increases in rates of substance use disorder and overdose in men (approximately 2.5 times the rate of women in 2019), racial minorities, and large urban settings [17, 18].

The overall incidence of endocarditis in PWID, though difficult to assess, is much higher than average. One study estimates up to 11.9 cases per 100,000 person years [19] in comparison to 1.4–6.2 cases per 100,000 person years in the general population [20]. Another estimate places the rate closer to 20-times that of the general population [21]. A recent international prospective endocarditis study found that among 11 centers sampled in the US with >500 IE cases, about 16% were IDU-related [20]. Europe and Asian Countries had about 9% associated with active intravenous drug use while South American had <1%. Slipczuk's systematic review complements these findings of a statistically significant increase in reported IDU-related cases in N. America from 17.3% in the 1980s to 50.7% in the 2000s consistent with the above noted rise in PWID due to the US opioid epidemic [22]. Meanwhile the rates of IDU-IE decreased in Europe in the early 2000s from 21.1% in the 1990s to 6.8%, $p < 0.01$). A recent Swedish study found a decrease in cases beginning in 2011 [23]. General IE is reported to affect males in 60–70% of cases [24] but there is a lack of systematic study on gender in IDU-IE. Studies performed since 2000 in the US generally have reported females as 30–55% of the patient population [25–27] which would be similar to slightly higher than the estimated proportion of females who inject drugs in North America. Further study is needed to determine the relative risk of endocarditis in male versus female PWID.

3. Right sided endocarditis in persons who inject drugs

Endocarditis of the tricuspid and pulmonic valves, or right-sided infective endocarditis (RSIE), is rarer than left-sided endocarditis and is classically cited as occurring in 5–10% of all IE cases [28]. Risk factors include IDU along with healthcare associated devices such as cardiac implants, hemodialysis catheters, and other long term venous access devices. The exact proportion of RSIE in PWID presenting with IE is difficult to determine as most reports on this topic are single center and/or retrospective in nature. In the late 1940s and 1950s, reports first began to be published of endocarditis in PWID making note of markedly higher proportions of tricuspid valve (TV) endocarditis and S. aureus involvement [29]. This phenomenon was met with scrutiny. A relatively large series by Cherubin et al. from 1960 to 1967 of 36 IDU-IE cases had TV involvement in 18% (9% sole TV, 9% in combination with another valve) [30]. While acknowledging that this is still larger than the 5–10% of TV cases seen in the non-injecting population, the authors proposed that the increased frequency of TV reports were due to either reporting bias or regional variation in drug use as many of the previous cases reported were from the Washington DC area [30]. Since this original debate in the literature many reports have gone on to find TV valve predominance in IDU-IE cases [31–40], but not all [27, 41–47]. The reasons for these differences and their meaning remain unclear. Some study populations are surgical populations which may bias towards left-sided disease. Studies in the 1980s through mid-1990s predominately were in HIV positive patients which may have confounded presentation. At least one study has suggested that the substance of use may influence the phenotype of endocarditis [48]. Within these limitations, all that can be said with certainty is that right sided-endocarditis remains over-represented in this population but left-sided endocarditis is also commonplace.

The pathology of RSIE is still not fully understood. The right side of the heart has lower pressures than the left and the valves are thus less prone to sclerosis and injury of the endothelium associated with high biomechanical forces. Injury to the endothelium of the right heart valves likely occurs through distinct mechanisms in IDU-IE. Some substances are directly toxic to endothelial cells and cardiomyocytes, particularly stimulants such as cocaine [49]. Particulate damage also plays a role. Most injected substances begin as powders or pills and may not fully dissolve in solution. Particulate matter is injected along with substances which bombards and disrupts the endothelium of the right heart before being filtered out by the lungs. Evidence suggests this is particularly true for pills which are crushed and injected with multiple reports of talc granulomas found within the lungs and heart valves of PWID [50, 51]. PWID are themselves aware of the potential damage from particulate matter and use a variety of devices ranging from medical grade filters to cigarette filters to strain their drugs; in many places filters are a provided as a component of harm reduction [52, 53]. There are no studies on whether filter use by PWID limits risk of IDU-IE.

Endothelium is naturally resistant to infection and even when damaged, only certain types and strains of bacteria with particular virulence factors can bind [54–58]. As bacteria adhere and invade, our immune system activates in an attempt to repair the damage and remove invaders. This results in an amalgam of fibrin and platelets being deposited in the area along with the bacteria resulting in a bacterial vegetation. An alternative sequence of vegetation formation involves the repair of injured valve endothelium by fibrin and platelets which form a sterile vegetation later seeded by a bacteremia. Indeed, some pathogens may lack virulence factors which would allow

them to bind directly to the damaged endothelium but which facilitate binding to the matrix of nonbacterial thrombotic lesions [58]. Regardless of event sequence, as this vegetation of platelets, fibrin, and bacteria grow the vegetation acts as a physical barrier protecting the embedded pathogens from immune regulation [59]. In addition, organisms at the center of the vegetation are concentrated at a higher density with fewer resources and go into a restricted growth phase which impairs the ability of antibiotics to eradicate them [60]. Finally, the nutrition deficiencies experienced by these deeper organisms that have been present longest in the vegetation develop morphological changes in cell wall thickness and increase their excretion of polysaccharides to form biofilms which further alter antibiotic susceptibility [61].

The distinctive pathophysiology of right-sided endocarditis combined with the low pressure, low biomechanical stress environment of right-sided vascular endothelium combine to alter the characteristics and risks of the endocarditis vegetation. The left-sided endocarditis literature tends to identify vegetations greater than 1 centimeter as being at increased risk of embolization and poor outcome [62]. This makes intuitive sense as a larger vegetation would be more friable while also being more subject to forces propelling it form the valve. However on the right side of the heart, vegetations measuring 2 to 3 cm are regularly described and the correlation between size and clinical outcomes is less clear [63, 64]. Vegetations ≥2 cm on right sided valves have been suggested to correlate with increased all cause mortality [63, 65] but evidence for this conclusion remains limited. Some of the lowered mortality for large vegetations in RSIE is due to the fact that unless a patent foramen ovale is present the vegetations embolize to the lung rather than the CNS; embolization to the CNS is an independent predictor of poor outcome. Another mitigating factor is the lower likelihood of heart failure with compromised right sided heart valves compared to left.

RSIE is more easily diagnosed by transthoracic echocardiogram (TTE) as the right-sided structures are located more anterior with a shorter distance between the transducer and structures [28]. Transesophageal echocardiography (TEE) is still superior to TTE for RSIE related to cardiac devices and has increased sensitivity for small vegetations and annular abscess. Endocarditis of the pulmonic valve or eustachian valve is also better visualized on TEE [28]. European and American guidelines indicate that TEE is not mandatory in isolated, native-valve, RSIE when TTE images are of high quality and risk of complication is low [62, 66]. In cases where TTE and TEE are unrevealing but high clinical suspicion remains, more advanced imaging techniques may be considered including 18F-fluorodeoxyglucose positron emission tomography/CT, cardiac CT, or radiolabeled white blood cells scintigraphy. This field of study continues to involve but studies indicated that these methods may have increased sensitivity in instances such as prosthetic infections and have the additional benefit of identifying silent emboli and aneurysms [66].

4. Population specific considerations

4.1 Women

Women who use drugs are more likely than men to develop clinical addiction and more rapidly progress to severe addiction [67]. Among those who seek treatment, women have higher opioid craving scores [68], psychiatric comorbidities [69], and physical health problems than their male counterparts [69, 70]. Given these differences, it is not surprising that women may also use their drugs differently. Some

studies have shown women are more likely to inject their preferred substance of abuse [71], are more likely to share needles and equipment [72], and possibly inject more frequently than males [73]. These behaviors increase infectious risk, including for IDU-IE. A retrospective study found that among HIV positive PWID, females had higher odds of IE with a multivariate OR of 3.26 (95% CI 1·73–6·14) [34]. A second study with 17 cases of IDU-IE found a similar trend but did not reach statistical significance (OR 1·62, 95% CI 0·61–4·34) [74]. Smaller/deeper veins resulting in more tissue damage during injection has been one theory proposed to explain this finding [34]. Another is the possibility for more rapid sclerosis of their smaller peripheral veins resulting in migration to high risk injection sites such as the jugular vein [75].

4.2 HIV population

HIV and endocarditis have overlapping risk factors and there are multiple studies assessing the outcomes of endocarditis in HIV positive persons. Early in the HIV epidemic it was feared that the cardiopulmonary bypass required for surgery could hasten the advancement to AIDS as a result of the general immunosuppression observed after major surgical procedures in combination with general anesthesia [76]. In the era of combined highly active antiretroviral therapy, studies indicate no worse outcomes in HIV positive patients requiring cardiac surgery compared to the general population [77]. A study by Ortega et al. in Spain found that the incidence of IDU-IE in persons living with HIV decreased with the advent of highly active antiretroviral therapy [78]. HIV does not seem to worsen the outcomes of IE unless severe immunosuppression is present with an AIDS defining condition and/or CD4+ cell counts <200/microL [79, 80]. A general trend corresponding to increased mortality with declining CD4+ count below 500 microL has been observed [81].

5. Endocarditis pathogens in persons who inject drugs

PWID have been found to have endocarditis with a wide variety of pathogens. Some atypical pathogens have been reported to be more common in this population due to a variety of factors including varied skin colonization patterns, risk imposed by the substances themselves, or through the agents used as solvents.

5.1 Methicillin resistant staphylococcus aureus (MRSA)

Staphylococcus aureus has been found to be the most common endocarditis pathogen in many industrialized countries but this shift with Staphylococcal predominance was first noted in those with IDU-IE [24]. S. aureus remains the most common pathogen implicated in IDU-IE. [82] PWID are estimated to be 16.3 times as likely to develop invasive MRSA infections that others. In a recent study assessing surveillance data from 6 sites across the US, the proportion of invasive MRSA cases that occurred among PWIDs increased from 4.1% in 2011 to 9.2% in 2016. Of these cases, 20% were IE. [83] Studies indicate that people who are colonized with S. aureus are at higher risk of infection [84] and additional studies indicate that PWID have high rates of colonization [84]. When they develop clinical infections with S. aureus it is with the specific strains with which they are colonized [85]. The exact mechanism for increased colonization and infection by MRSA in PWID is unclear. It may be that the nature of shared drug use environments, crowded and unsanitary conditions,

and frequent healthcare center exposures may lead to transmission of S. aureus in this community. [86] Repetitive disruption of the skin barrier can then enable deep seated infections including IDU-IE.

Right-sided disease accounts for about 66% of IDU-associated S. aureus endocarditis [87, 88]. There are also studies that show a relatively high rate of multivalve S. aureus infection compared to people who do not inject drugs. [87] The mortality rate of S. aureus endocarditis in PWID is lower than in people who do not inject drugs which is thought to be due to younger age and fewer comorbid conditions [39, 87, 89, 90]. Embolic events generally occur at a higher rate with S. aureus IE compared with IE due to other pathogens [91, 92]. Studies usually report a lower rate of surgery for PWID with S. aureus IE than in people who do not inject drugs. Current treatment guidelines recommend treating S. aureus associated endocarditis with 6 weeks of therapy [62].

5.2 Candida

IE due to candida species is relatively rare, accounting for around 2–4% of all cases [93, 94]. Multiple outbreaks of disseminated candida infections have been traced back to using lemon juice as a solvent for intravenous heroin and cocaine [95–97]. Acids such as lemon juice are commonly used to dissolve brown heroin, which is a base form less water soluble than the white, salt form of heroin. Similarly the crack form of cocaine is prepared for injection with the addition of an acid [98]. Lemon juice has been shown to readily grow Candida at room temperature, and the belief is that the resultant infection is due to injection of a high inoculum of Candida by PWID [95]. These disseminated candida infections have a predilection for endogenous spread to the eye, with resultant endophthalmitis in addition to endocarditis. Sterile packages of ascorbic acid are provided in many harm reduction centers to minimize the risk of Candida infections. Current treatment guidelines for native valve Candida IE recommend initial management with lipid formulation amphotericin B with or without flucytosine or a high dose echinocandin. This is then followed by step-down therapy with an azole. Valve replacement is recommended, and long term suppression is recommended for patients who cannot undergo valve replacement followed by chronic suppression [62].

5.3 Non-HACEK gram negatives

Compared to the general population, PWID are at increased risk of non-HACEK gram negative endocarditis though this is still a rare clinical entity [99, 100]. A recent single center study from the southeast US identified 43 cases of gram negative IE, of which 93% had a history of or active injection drug use [101]. In other recent studies nosocomial acquisition was a more common risk factor than IDU [100, 102]. In the US study the majority of these patients had had a prior instance of IE and most cases were of native valves, predominately right-sided valves. Of these cases, 68% were associated with Pseudomonas aeruginosa, 20% Serratia marcescens, and the remaining were with Enterobacter cloacae, Klebsiella oxytoca, and Acinetobacter baumannii. These patients were very ill, with 60% requiring a stay in the intensive care unit during their hospitalization and roughly 25% underwent valve surgery; the 12 month all-cause mortality rate was 30%. This is consistent with the overall 20–30% mortality seen in IE caused by non-HACEK gram negative bacilli though this mortality rate encompasses a wide range of patient populations with many having multiple underlying comorbidities. [103]

Pseudomonas is one of the most common non-HACEK organisms cited in this group [104]. The major source of Pseudomonas IE appears to be contaminated water used to mix drugs for injection and this may explain the presence of other water organisms such as S. marcescens as well [105, 106]. In a Pseudomonal endocarditis outbreak in Detroit occurring in the 1970s–1980s associated with injection of dissolved pentazocine and tripelennamine ('Ts and blues'), the drug itself was found to act as a selective culture medium which inhibited the growth of S. aureus and many pseudomonas strains but not serotype O11 strains which were associated with the invasive infections [107]. S. marcescens is increasingly being reported in US literature as well though the exact association or cause of this increase remains unclear [106, 108]. One factor that may select for gram negatives in this group is intensive or frequent therapy for gram positive bacteria that cause skin abscesses and more frequent deep-seated infections thus resulting in selective pressure. Evidence for this is found in the high rate of gram negative bacilli (and Candida) blood stream infections found in persons who continued to inject while on therapy for predominately gram positive infections [109]. Evidence for management of infections by these organisms is limited and current treatment guidelines recommend consideration of surgical management in addition to dual antibiotic therapy for 6 weeks. Proposed combinations are a beta-lactam in combination with either a fluoroquinolone or aminoglycoside [62].

5.4 Others

There are innumerable case reports describing unusual pathogens isolated in this patient population, frequently in the setting of polymicrobial infections [110, 111]. This includes non-tuberculous mycobacteria which should be considered as a possible cause of culture negative endocarditis [112]. Speical blood culture medium is required for acid fast bacteria and they may still be difficult to culture with a long window between collection and resultant growth. Endocarditis secondary to unusual or fastidious oral flora, including Neisseria sicca and anaerobes such as Veillonella sp., have been in described in this population in association with those who lick their needles prior to injection [113, 114]. Given the paucity of treatment evidence for severe infections with these types of organisms and the increased mortality associated with polymicrobial infections, treatment is individualized and outcomes with these types of organisms and infections is frequently higher than average.

6. Treatment difficulties of IDU-IE

6.1 Antibiotic delivery and oral antibiotics

How to best provide prolonged intravenous therapy to PWID is a particularly perplexing issue. Concerns regarding discharge with an intravenous line include potential use of the catheter for drug injection, seeding the line with transient bacteremia even if the line itself is not used to inject, and difficulty finding home health companies for this population. Countries over the world have different outpatient parenteral antibiotic therapy (OPAT) systems and healthcare delivery models making this topic even more difficult to analyze. Antibiotic delivery models include infusion at ambulatory care centers or in the home by home care nurses (more common in European countries) or discharge of patients home to administer their own parenteral antibiotics with only weekly home health oversight (the US). These differing models with variable

degrees of patient oversight result in differing risk of discharge of PWID with a central catheter. Some studies have shown OPAT can be done relatively safely in PWID, but these studies contained a large proportion of persons retained in a facility of some type or were noted to require particularly intensive oversight [115]. Given the difficulties and challenges of this group, many health facilities retain their population with IDU-IE inpatient or at an affiliated facility for the duration of their treatment [116]. This strategy is frustrating for patients and uses large amounts of healthcare resources. IDU-IE in the US was recently estimated to have direct costs of $180,000 and cost significantly more than IE attributed to causes other than IDU [117].

For all of these reasons, short course and oral therapy are very attractive options. Studies show that 2 week courses of IV beta-lactam therapy in isolated tricuspid valve IE secondary to methicillin susceptible S. aureus (MSSA) with no embolic phenomena outside of the lungs can be successful. Multiple studies have evaluated this strategy over time predominately with the use of cloxacillin [118]. Addition of an aminoglycoside was not found to significantly alter outcomes in one study though most studies evaluating this short-course strategy evaluated the beta-lactam in combination with an aminoglycoside [119]. These studies were generally performed when co-administration of aminoglycosides was routine and recommended for S aureus IE. This is no longer the case and the most recent American guidelines discourage the use even in right-sided endocarditis [62]. Evidence indicates that the use of a glycopeptide for short course therapy such as would be required for MRSA is not efficacious even when combined with an aminoglycoside [120].

Oral antibiotics offer even greater appeal. In 1989 Dworkin published 14 cases of right sided, S aureus IDU-IE treated with ciprofloxacin and rifampin [121]. Heldman et al. then completed a randomized control trial of oxacillin/gentamicin compared to ciprofloxacin/rifampin in 85 right-sided IDU-IE patients; 41 did not complete therapy and only 44 were analyzed. There were three failures in the standard arm and one in the oral arm. While these results are reassuring, they may not be fully generalizable to today's population. Between these two studies only 15% had pulmonary emboli and only 28% with echocardiograms had visible vegetations. While this may in part reflect limits of older echocardiographic technology, those caring for populations with visible vegetations must be wary. Large vegetations are those which are most difficult to treat due to the organism density and limited antibiotic penetration into vegetations [122–124]. Additionally, only 5% of Heldman's population had MRSA. PWID are more prone to MRSA infections which are likely to be fluoroquinolone-resistant [83, 125].

The most important development is the POET trial which randomized 400 left-sided IE patients to a full course of intravenous therapy or changeover to oral therapy [126]. This study included those with cardiac implantable electronic devices (CIEDs), prosthetic valves, and surgical patients and still found that changing to oral therapy was noninferior to full intravenous courses. Generalizing to our IDU-IE population, however, again requires caution. Fewer than 6% of patients had a vegetation >9 mm at the time of randomization. IDU-IE patients with right-sided disease may be less likely to undergo surgery and have large vegetations. More importantly, this population predominately suffered from streptococcal disease. None of these patients had MRSA and the MSSA was highly susceptible, even to penicillin. Doses used for these regimens were much higher than is typically seen such as using 600 mg PO BID of rifampin. This results in a need to ensure that a patient can orally tolerate the medications and that a way to monitor for toxicities of the oral antibiotics is available including office follow-up and blood tests. For this reason those who were deemed unreliable were excluded and only five PWID were included in this study.

In summary, there is increasing and high grade evidence for the safety and efficacy of oral antibiotics in the treatment of endocarditis including IDU-IE but caveats remain. There is very little data on the safety of oral therapies when vegetations are greater than 1 cm in size or where there is extensive co-occurring embolic phenomena. Parameters to guide the frequency of blood testing for safety monitoring on these regimens is lacking and frequent outpatient blood draws in PWID may be further complicated by venous sclerosis and poor venous access. Evidence on orals for treatment of MRSA IE is lacking. Invasive MRSA infection is more common in PWID so this is of particular relevance to this group [83]. Follow-up publications have noted the mutation of methicillin resistance should not affect the function of non-beta-lactam antibiotics and thus regimens which do not rely on this class of agents should be as effective against MRSA as MSSA [127] but clinicians remain cautious.

It must be noted that while the evidence above provides evidence for the option of oral antibiotics and outpatient treatment, multiple additional factors must be incorporated into clinical decision making. The need for complete adherence to a complex medical regimen and close outpatient follow-up may be inherently problematic in this population. Socioeconomic complications including unstable housing, lack of transportation, and unreliable phone service may make care in the outpatient setting untenable. And then there is the risk of ongoing drug use once discharged. This would not only further impair follow-up but risk renal/hepatic injury while on renally-dosed medications, worsening of the current infection, and possible development of a new suprainfection. Each patient will require nuanced and thoughtful decision-making to determine the best treatment course for an individual and their unique set of factors. This precludes the development of any one 'rule' on how to manage this group and practice is likely to remain heterogeneous across institutions and providers.

6.2 Surgery

Perhaps the most difficult aspect of IDU-IE is weighing the risk–benefit of surgery. This group is relatively young. Bioprosthetic valves avoid the need for anticoagulation but are less durable than mechanical valves resulting in higher rates of repair surgeries over time [128]. The main concern, however, is that the patient will re-infect the heart valve through ongoing substance use. Addiction is a chronic, relapsing disease with heroin relapse rates following simple detox as high as 91% [129]. Ongoing injection drug use raises the risk for prosthetic valve endocarditis which has worse outcomes than native valve endocarditis [130]. What timing, surgical approach, and mitigating factors can identify patients who would individually benefit from surgical rather than medical management remain vastly understudied. Benefits of surgery in isolated tricuspid valve endocarditis are the least-well resolved. These concerns have led to significant debate regarding risk-stratification and performance of cardiac surgery in PWID. With the lack of clear guidelines or risk stratification protocols, there is wide variability in surgical management. Some surgeons are only willing to perform a single heart operation while others mitigate their responses by what kind of SUD treatment was available and attained by the patient [131–133].

To help guide clinical decision making, multiple studies have attempted to provide objective assessment of outcomes for those who undergo surgery for IDU-IE but only a small number have compared the outcomes to a contemporaneous population of routine IE. In the English based literature of the last 2 decades, at least 7 US, 2 Swedish, 1 Czech Republic, 1 Italian, 1 international prospective study, and 2 meta-analyses have been published comparing surgical outcomes in IDU-IE to the

general IE population [27, 35, 43–45, 47, 134–140]. These comparisons must be taken with a grain of salt given that the compared groups differ in demographics, valve characteristics and pathogen type while also having very different proportions of pre-existing comorbidities. Surgical selection bias also will play a role in determining the timing and type of surgical intervention within and between groups. With these caveats in mind, all of these studies have come to the same conclusion: the in-patient and 30-day mortality of this population is comparable to or better than those undergoing surgery for non-IDU-IE while longer term mortality appears higher. Thalme et al. found that for those undergoing surgery for left sided IE, PWID had significantly higher mortality in the first 5-years despite comparable to better in-patient mortality; none of the 5 surgical patients in the IDU-IE group were alive at 4 years [35]. Rabkin et al. who assessed 197 surgical endocarditis cases including 64 PWID defined as *ever* having injected drugs [44] found on Cox regression analysis that PWID had lower ten-year survival (41·1% IDU vs. 52% non-IDU, p = 0·03). Ongoing substance use has been found to be the primary driver of this increased long-term mortality in at least one study [141].

These studies also have come to the same broad conclusion that repeat infective endocarditis is more common in this group though exactly how much more common varies across studies. Thalme found the odds of recurrent endocarditis in PWID was 6-fold higher (12·5 vs. 2·3%, OR 6·07, p = 0·007, 95% CI 1·55–23·70). This aligns with the findings of Kim et al. who found a propensity score matched HR of 6.2 for reinfection in PWID compared to general IE (95% CI 2·56–15, p < 0·001). The studies by Kaiser and Shrestha assessed a combined 858 surgically treated IE patients of whom 93 were PWID [43, 45]. Both found significantly higher rates of reinfection in PWID (HR 9·8, 95% CI 2·7–35·3 in Shrestha and 17 vs. 5%, p = 0·03 in Kaiser) [43, 45].

Descriptions of repeat IDU-IE cases are limited despite being relatively common. It appears that repeat infection occurs relatively quickly. In a study of 87 IDU-IE patients surviving their primary hospital stay, 25·7% developed repeat IE within a median of 257 days [142]. Kim et al. found the median time to reinfection was18·1 months [27]. The microbiology is more varied on repeat endocarditis admissions: whereas 95% of one center's patients had S. aureus as the causative pathogen on their first episode, it accounted for only 54% of cases on the second episode where Candida, Enterococcus, and Streptococcus were more common [142]. Finally, repeat endocarditis predisposes to higher mortality. The ICE found that 20% of all IE patients who suffered a recurrent episode were deceased at 1 year compared to 9% surviving a single episode [143]. This difference seems even more profound for IDU-IE as 36% of those with a repeat case were deceased at 1 year vs. 4% of those with a single episode [142]. It is possible that re-infection is a marker of more severe opioid use disorder which then drives the higher mortality rather than the IE itself but these factors are difficult to disentangle.

Medical research has a long way to go in determining how much benefit an individual with IDU-IE is likely to receive by undergoing surgical rather than medical treatment and how to parse that risk in real time. At this time, surgical thresholds vary across countries, institutions, and individual surgeons but the medical literature strongly suggests that when a patient does undergo surgery, they achieve short term survival comparable to their non-IDU-IE peers. Long term outcomes and what role, if any, they should play in acute surgical decision making are more difficult to parse.

7. Areas of exploration: the future of IDU-IE

Given the difficulties noted above, new strategies for treating this group are urgently needed. Some promise lies in the areas of novel antibiotics, novel surgical approaches, and the rise of more integrated addiction care.

7.1 Lipoglycopeptides

The lipoglycopeptides have a long, lipophilic side chain added onto glycopeptides (the class of vancomycin and teicoplanin). The result is similar bactericidal activity but the more lipophilic side chain anchoring onto the bacterial cell membrane results in increased potency and, potentially, half-life [144]. Telavancin, oritavancin, and dalbavancin are all FDA approved for treatment of complex skin and soft tissue infections and Telavancin additionally is approved for pneumonias. The dosing of telavancin is daily while dalbavancin and oritavancin can be dosed weekly.

Telavancin and Dalbavancin currently have the most promising data for endocarditis. Telavancin has been shown in multiple in vitro studies to be at least as effective as daptomycin and vancomycin [145]. In 2010 telavancin was successfully used to treat right sided, native MRSA endocarditis. The patient remained culture positive after 8 days of vancomycin. He was then changed to telavancin with negative cultures resulting in 24 hours [146]. Since then telavancin has been used to successfully treat MRSA mitral valve endocarditis [147] and VISA CIED endocarditis [148].

Dalbavancin also has endocarditis data [149–151]. In the rabbit IE model it was shown that dalbavancin was 2–4-fold more potent than vancomycin [152]. One of the first human endocarditis case was attempted treatment of MRSA native valve endocarditis in a pregnant PWID. She was treated with vancomycin and then daptomycin 10 mg/kg for the first 26 days. Unfortunately there were two treatment interruptions where the patient left against medical advice; after returning from the second interruption she received a 1 g loading dose of dalbavancin followed by 500 mgs weekly for a total of 4 weeks. Unfortunately, she presented to the hospital 11 days after her final dose with S. aureus bacteremia that was now vancomycin intermediate (MIC 4 mcg/mL) and telavancin resistant. It was hypothesized that increased renal filtration and altered protein binding of pregnancy may have decreased the half-life of the drug leading to subtherapeutic levels.

More positive outcomes were found in a 2 year, retrospective study of 24 IE patients transitioned to dalbavancin after clearing their blood cultures on standard care; three patients were started directly on dalbavancin. Causative organisms included S aureus, streptococci, Enterococcus, Aerococcus, and coagulase-negative Staphylococcus. Drug regimens were a 1 g load with 500 mg weekly thereafter and a 1·5 g load with 1 g twice weekly. Mean duration of administration was 6 weeks but ranged from 1-30 weeks. A patient with E faecalis prosthetic valve infection died of surgical complications and another patient failed treatment. This patient had an MRSA CIED infection which could not be fully removed. The patient received 30 weeks of Dalbavancin but then had breakthrough bacteremia. The breakthrough strain showed small colony variants with a vancomycin MIC of 2 mg/L (up from 1 mg/L).

A similar cohort by Wunsch et al. treated 25 endocarditis cases which included 6 prosthetic valves and 4 CIEDs with a similar pathogen cohort [153]. Patients were switched to dalbavancin after having been treated initially with more routine antimicrobials. Nine of the patients received a single 1.5 g dose while 8 received a dose of 1 g

on day 1 followed by 500 mg on day 8. Successful treatment was achieved in 92% of patients. The patient who failed treatment died of sepsis from MSSA IE.

Use in IDU-IE has had mixed results due to the difficulty in maintaining this population in treatment. A study of 9 persons with right sided IDU-IE found that only 3 of the patient completed the pre-defined treatment course [154]. Of those with a successful completed course, 2 received a planned single dose and 1 received a planned 2 doses; 4 of those who failed to complete their course were planned to receive only a single dose which highlights the difficulty. Also the most concerning issue to arise from these studies is the potential for resistance. Both the case of the pregnant female and the CIED infection suggest suboptimal treatment can result in rising MICs for vancomycin as well as the lipoglycopeptides. This could conceivably be a problem in PWID who may not return for their follow-up medication doses.

7.2 Delafloxacin

Delafloxacin is a novel fluoroquinolone marketed by Melinta under the brand name Baxdela currently FDA approved for skin and soft tissue infections. A major limitation of oral therapy for endocarditis noted above is MRSA's frequent resistant to fluoroquinolones. However, delafloxacin currently is estimated to have efficacy against 88% of US MRSA strains [155], including those resistant to other fluoroquinolones. This is due to the fact that delafloxacin binds to both the topoisomerase and gyrase in relatively equal amounts whereas other fluoroquinolones tend to more heavily target one enzyme over the other. The result is a lower likelihood of 2 spontaneous mutations developing and lower risk of resistance [156]. This combined with its relatively unique ability to maintain efficacy in acidic environments [156] may allow it to overcome severe MRSA infections such as endocarditis where other oral agents have failed.

7.3 Bacteriophages

The use of lytic bacteriophages as antibacterial therapy has long been hypothesized but clinical studies are in their infancy [157]. To date few persons have been treated with a bacteriophage and only when all other alternatives had been exhausted. The bacteriophage generally must be matched to the pathogen with some pathogens having resistance and repeated testing to assess for acquired resistance with treatment is recommended [158]. Expanded use of phage therapy holds promise for treatment of resistant microorganisms, difficult to treat microorganisms such as MRSA, and device related infections where biofilm plays a significant role in pathology. Endocarditis with its vegetation could fall into the latter group. At least one animal study shows possible synergistic effect between phages and antibiotics for endocarditis treatment [159] and at least seven persons have received adjunctive phage therapy for endocarditis due to S. aureus [160, 161]. The patient seemed to have ongoing clearance and control of the infection with a negative PET on day 80 however ongoing severe heart failure persisted and the patient ultimately expired. What role the phage therapy played as compared to the antibiotics is undetermined. Phage therapy could provide an attractive alternative for those with IDU-IE as it might allow for effective treatment of larger vegetations thereby further limiting the need for surgery. Heightened efficacy may also allow for shorter treatment courses for this condition. Challenges to progressive study in this particular disease state includes the relative rarity of endocarditis, the rapid progression of most endocarditis cases making interventional

studies or the matching of phages to pathogen more logistically complex, and the current reserved use of phages only for patient where no alternatives exist.

7.4 Percutaneous aspiration

Percutaneous aspiration of vegetations from the tricuspid valve has been reported with increasing frequency in the last decade [162, 163]. This procedure is performed by placing the patient on an extracorporeal circulatory circuit through large bore venous drainage and venous return cannulas. Under transesophageal echocardiographic guidance, the vacuum-assisted device is frequently performed with use of the AngioVac system, a product of Angiodynamics, USA. The goals of vegetation aspiration are decreased bacterial load, decreased vegetation size to lower embolic risk and antibiotic failure risk, and possibly to limit progressive damage to the valve and cardiac structures. Patients with vegetations greater than 1 cm in size and outside of criteria used in common oral endocarditis treatment studies may become eligible for oral treatment therapies as compared to intravenous following angiovac debulking which may be associated with decreased length of stay and healthcare costs. Prospective and controlled studies on the benefits and risks of this procedure are not yet available but will hopefully be performed in the coming decade.

7.5 Co-addiction treatment

Substance use disorder is a chronic disease making its stabilization and management in the acute care setting challenging. In many instances the substance use disorder is disregarded while the acute condition is treated resulting in problematic disconnect [164]. The first is that patients can withdraw while in the inpatient setting. This can result in increased risk of leaving against medical advice, ongoing substance use during the hospital stay, and increased conflict between provider and patient [165]. Where specialized addiction professionals are unavailable, hospitalists and internists should be familiar with the medications used to treat substance withdrawal and substance use disorders. This will then allow providers to take full advantage of a potential 'teachable moment'. Facilitating detox from substances and intake to treatment is crucial for long term health. A randomized clinical trial found that those who began medication-assisted therapy with buprenorphine while inpatient were significantly more likely to enter treatment post-discharge (72 vs. 12%, $p < 0{\cdot}001$), be engaged in treatment at 6 months (16·7 vs. 3.0% $p = 0{\cdot}007$), and have less illicit opioid use in the 30 days prior to a 6-month interview (incidence rate ratio 0·6, 95% CI 0·46–0·73, $p < 0{\cdot}01$) [166]. Unfortunately, this same study found no significant difference in injection opioid frequency at 6 months among PWID despite the fact that the odds of injection opioid use were 4·57-times higher on days without buprenorphine than with buprenorphine. The authors hypothesized that this specific group might need higher doses to combat more severe addiction and that the new long-acting injectable buprenorphine may improve outcomes [167]. It is worth noting, that reduction in injection frequency, even without full cessation, is associated with decreased risk for invasive bacterial infection [168].

8. Conclusions

IDU-IE remains a distinct entity that is encountered across the globe. In places such as the US there have been great increases in the incidence and prevalence of this

disease. Yet the ideal management of this patient population remains understudied and under debate. Ongoing research to identify which patients have the highest benefit from surgical intervention in RSIE are needed. The use of percutaneous aspiration and novel medication such as the lipoglycopeptides provide alternatives to traditional treatment models with increasing use. Most important of all is the need for progressive integration of addiction care into acute care medical management in order to treat the root cause of IDU-IE and achieve long term positive health outcomes.

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