



Review article

Management of endocarditis among persons who inject drugs: A narrative review of surgical and psychiatric approaches and controversies

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ABSTRACT

Background: People who inject drugs (PWID) represent a high-risk subgroup of endocarditis patients. This is highlighted by poorer post-operative outcomes in injection drug use-related infective endocarditis (IDU-IE), which is largely attributable to the increased vulnerability of prosthetic valves to re-infection. Consequently, many centres do not perform valve replacement on these patients. A parallel, but often underrecognized, component of care is the role of multi-disciplinary management for individuals with IDU-IE, including perioperative addictions and psychiatric care. Consequently, surgical management options in IDU-IE remain a controversial topic.

Objectives: To determine the characteristics of optimal surgical and psychiatric care for individuals with IDU-IE.

Methods: We conducted a narrative synthesis of the findings of literature retrieved from searches of computerized databases, hand searches, and authoritative text, organizing the findings into several key themes: clinical characteristics and factors associated with mortality in IDU-IE, alternative surgical management options, perioperative risk stratification techniques, principles of psychiatric and addictions management in IDU-IE, ethical considerations and controversies, and future research directions.

Results/conclusions: Managing IDU-IE involves the treatment of two comorbidities: the intra-cardiac infection and the underlying substance use disorder. Cardiac surgery represents a high-intensity intervention with appreciable risk, and the benefit it is not always clear. As patients often present acutely, it is not feasible to use drug abstinence as a prerequisite to surgery. Involvement of inpatient psychiatry and addictions teams, however, appears to be an evidence-based approach that can bridge IDU-IE patients with opioid agonist therapy in hospital and adequate outpatient treatment options for their underlying addiction upon their discharge from hospital. It is likely that a majority of these patients are not receiving optimal psychiatric management despite increasing recognition of efficacy. Further interdisciplinary studies are needed to elucidate optimal surgical and multidisciplinary protocols.

Background: Infective endocarditis (IE) is an infection of the innermost lining of the heart often affecting the heart valves. Over the last few decades, the epidemiology of IE has shifted in the developed world and while it continues to be a significant cause of morbidity and mortality, there has been a significant increased incidence among persons who inject drugs (PWID). To date, well-conducted epidemiologic studies of IE among PWID have been sparse, which has limited our ability to fully characterize this disease phenomenon. To address this knowledge deficit, we conducted a narrative synthesis of the findings of literature retrieved from searches of computerized databases, hand searches, and authoritative text, and organized our findings into six key themes: clinical characteristics and factors associated with mortality in IDU-IE, alternative surgical management options, perioperative risk stratification techniques, principles of psychiatric and addictions management in IDU-IE, ethical considerations and controversies, and future research directions.

1. Clinical characteristics and factors associated with mortality in IDU-IE

Persons who inject drugs (PWID) are predisposed to injection drug use-related infective endocarditis (IDU-IE) for a variety of reasons. The incidence of IDU-IE is 1.5 to 4 cases per 1000 years of IDU [1,2]. A recent American study found that the proportion of IE hospitalizations from IDU-IE increased from 7% to 12.1% between 2000 and 2013, particularly among 15- to 34-year-olds (27.1%–42.0%; $P < .001$) and

among whites (40.2%–68.9%; $P < .001$) [3].

The majority of the published literature in this population has focused on injected opioids, however, recent studies [4–6] have measured the relative breakdown of the primary substances used by PWID with endocarditis: opioids (67%: heroin [29%], morphine [29%], hydro-morphone [5.3%], oxycodone [1.3%], buprenorphine [2.6%]), methamphetamines (26.3%), bath salts (5.3%), cocaine (16%), and unknown type (11.2%).

PWID are at increased risk of IDU-IE chiefly due to IDU-mediated

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endothelial damage to the tricuspid valve, differences in infectious agents, and IDU-associated immunologic changes [7]. Although > 90% of all cases of IE are left-sided, the majority of IDU-IE (76%) are right-sided, and the majority of right-sided IE are IDU-related [1,2]. More than half of all IDU-IE involves *Staphylococcus aureus*, followed by Streptococci and enterococci, and less commonly, fungi and gram-negative bacilli [1,2]. As these organisms are responsive to intravenous (IV) antibiotics 70% of the time, culture-directed IV antibiotic therapy remains first line treatment for IDU-IE; however, PWID tend to require prolonged admissions, and many centres do not allow home IV antibiotic therapy in PWID [8]. Though there have been attempts to utilize short, two-week courses of IV antibiotics, not all patients are candidates for this approach: those with methicillin-resistant *S. aureus*, renal dysfunction, intolerance to aminoglycosides, large vegetations or hemodynamic compromise are best managed with at least four weeks of antimicrobial treatment [9].

Even with optimal medical therapy, between 20 and 40% of patients with a first-episode of IDU-IE will ultimately require surgical intervention [4,5,10]. However, more than half of those who undergo valve replacement surgeries will require repeated surgical intervention due to persistent injection of drugs [4,11,12]. The indications for surgery in patients with IDU-IE are generally the same as for other patients with IE, and includes failure of medical management, refractory heart failure, infection eroding into non-valvular cardiac structures, presence of vegetations with significant embolic risk, valvar obstruction, unstable prosthesis or prosthetic valve IE, neurological complications, and fungal or difficult-to-treat microorganisms [10,13]. The aims of surgical intervention in IDU-IE are to eradicate infection and restore valvular function and cardiac integrity.

Individuals with IDU-IE generally experience worse post-operative outcomes than in those with non IDU-IE [4,11,12]. This discrepancy has been largely attributed to the increased vulnerability of prosthetic valves to re-infection given the high rate of IDU recidivism in PWID [4]. However, there are significant variations in reported figures across studies, largely depending on the type of IDU-IE and the patient sub-population. Patients with tricuspid valve IDU-IE tend to have a lower case fatality rate than patients with aortic or other forms of IDU-IE [14–17]. In-hospital mortality rates following valve replacement have approached upwards of 20% [12]; however, recent Canadian literature has indicated the two-year mortality rate of patients with IDU-IE is up to 30% [18]. In a retrospective study of 220 cases of IDU-IE involving right-sided native valves, the overall mortality was approximately 6% [19]. In this same study, the size of the vegetation (> 2 cm) and fungal etiology were found to be the strongest predictors of mortality in IDU-IE, increasing the odds ratio of death by 10- and 46-fold, respectively [19].

A recent meta-analysis of tricuspid valve IDU-IE demonstrated an increased risk of recurrent IDU-IE and reintervention in the replacement group, though this did not translate to long-term mortality differences [22]. Recent studies have indicated that bioprosthetic and mechanical valves are associated with similar survival and freedom from IE recurrence, supporting the notion that patient factors ought to guide prosthesis choice in IDU-IE [23]. While IDU-IE patients' comparatively young age increases their predisposition to structural valve deterioration, traditional explanations for the similar outcome have included reduced adherence to long-term anticoagulation and limited life expectancy compared to age-equivalents in the general population [22]. In the case of aortic root replacement, homograft may provide an advantage with respect to prevention of recurrence due to increased uptake of IV antibiotics [22,23].

2. Alternative surgical management options in IDU-IE

Justifiable concerns have been raised regarding the advisability of implanting prosthetic valves in patients with right-sided IDU-IE due to its heightened susceptibility to reinfection [19–21]. As a result, an

emerging body of surgical literature has explored the utility of non-replacement strategies in IDU-IE.

Tricuspid valvectomy has been proposed as a prosthetic-free bridge to drug abstinence or as destination therapy, however, it is rarely performed in the modern era as both early and late right heart failure is common [26].

More recently, endovascular vegectomy, particularly for the tricuspid valve, has been successfully reported in a few case reports and series [27–31]. In addition to use in the elective setting, endovascular vegectomy may have a role as a bridge to addictions recovery in IDU-IE [31]. The technique is performed using the AngioVac [33] venous drainage cannula, which is advanced to the right atrium via femoral venous access; then, the cannula is connected to a veno-venous cardiopulmonary bypass circuit and filter. Vegectomy is then performed under intraoperative transesophageal echocardiographic guidance. The procedural endpoint, as defined by George and colleagues, is determined when > 1 cm of vegetation is retrieved and/or no further material can be isolated [34]. Among this series, 72% of the patients had confirmed history of IDU. Following the procedure, 85% had resolution of their bacteremia, however 9% still required surgery and 9% did not survive. Coagulopathy, including disseminated intravascular coagulopathy, was a significant concern given the high burden of Hepatitis C in this group [34].

Percutaneous vegectomy has also been used successfully among PWID with infected device leads, and appears to be an effective strategy if the patient with IDU-IE is not a candidate for valve replacement [35,36].

3. Perioperative risk stratification in IDU-IE

Although many have attempted to develop perioperative risk stratification tools, there are no specific protocols for individuals with IDU-IE [37]. Gatta and colleagues combined preoperative anemia, New York Heart Association Class IV status (NYHA-IV), critical status, presence of significant intra-cardiac destruction, the need to operate on the aorta, and an aortic cross clamp time exceeding 150 min to create an internally-validated, 6-item score to predict intra-hospital mortality in individuals with IE [38]. Gaca and colleagues combined urgency status, cardiogenic shock, renal failure and insulin-dependent diabetes to predict a composite outcome of major morbidity and mortality [39]. De Feo and colleagues found renal failure, NYHA IV and perivalvular involvement to be important predictors of early mortality [37]. The International Collaboration on Endocarditis (ICE) has established a multicentric database to study the epidemiology of IE in greater detail. A recently published study of left-sided IE concluded that surgical decision making in IE is largely consistent with established guidelines, and that nearly 25% of ideal candidates do not undergo surgery; however, as < 5% of the total cohort had a history of IDU, it remains unclear if these findings can be extrapolated to IDU-IE [40].

The Society of Thoracic Surgeons IE post-operative risk score provides prognostic information for survival beyond the operative period; therein, infection with *Staphylococcus aureus* is associated with non-surgical management [38]. A large multicentre Italian study developed a logistic risk score of 13 factors associated with early mortality after IE surgery (EndoSCORE) [42], however, the proportion of patients with IDU history was not determined. Furthermore, the salient risk factors of the EndoSCORE are similar to those identified by previous studies (age > 80 years, number of affected valves > 2, preoperative shock, pseudomonas and fungal infections) [41].

Limitations of existing risk scores include the unknown generalizability of single-centre scores, the inability to distinguish by organism type, the inability to discriminate between prosthetic and native valve IE, and the inability to extrapolate to PWID [37,38]. Although De Feo and colleagues found microorganism species to be a predictor of mortality, this was not included in the final score, and the score itself only investigated early outcomes [37]. Notably, while scoring systems

correlated drug use with higher surgical risk, there are currently none which stratify risk within this group, and the predictive features of comorbid substance use disorders, although likely a critical outcome predictor, are not well-established [37]. Importantly, much of the surgical literature fails to characterize patients' concurrent psychiatric management, if any, into perioperative risk stratification [42].

4. Principles of psychiatric and addictions management in IDU-IE

Optimal management of patients with IDU-IE involves the treatment of two comorbidities: the intra-cardiac infection and the underlying substance use disorder. Thus, improving long-term perioperative outcomes in patients with IDU-IE involves harmonizing medical, surgical, psychiatric and addictions care [44]. However, it is not always easy to address underlying psychiatric and addictive disorders, especially during high-acuity situations, which are common in the intoxication-withdrawal cycle frequently observed in addiction. As a result, many cardiac surgeons consider the absence of a desire to discontinue drug use to be a surgical contraindication, with some attempting to utilize signed drug contracts to enforce abstinence; however, this practice is both controversial and ineffective [45,46].

A more evidence-informed and effective approach involves inpatient collaboration with psychiatry and addictions specialists to develop a biopsychosocial formulation of the patient with IDU-IE [43,47]. Formulation involves exploring the fundamental reasons why a particular patient is predisposed to developing a medical problem. In IDU-IE, this involves psychiatric comorbidity, addictions history, psychological insight, access to services, and social supports, in order to develop a comprehensive understanding of the patient [42]. Individuals with six or more adverse experiences in childhood have a 46-fold increase in their likelihood of developing a substance use disorder [48]. For example, prior abstinence, engagement with addictions therapy, and insight are positive prognostic (or protective) factors [48].

Among the most important roles of the psychiatrist in the management of patients with IDU-IE is assessing and enhancing the patient's motivation for change – with abstinence or harm-reduction often serving as common goals. This is achieved using an evidence-based approach called Motivational Interviewing (MI), which is a non-judgmental conversational style developed by psychologists William Miller and Stephen Rollnick [49]. MI combines concepts from the trans-theoretical model of change with elements from the theory of cognitive dissonance, and primarily involves skillful, reflective, and non-judgmental interactions between client and therapist [50].

Although MI is most effective during the precontemplation and contemplation stages of change, it can be initiated at any point in treatment and can be delivered in multiple settings [51,52]. In many centres, the standard of care involves the immediate consultation of an inpatient addictions team, which has been shown to significantly increase the likelihood that the patient will engage with outpatient treatment, which in turn lessens the likelihood of relapse [53]. As most psychiatrists and addictions specialists have training in MI, consultations readily bridges patients with the initiation to recovery. MI can be readily combined with other harm-reduction approaches, including supervised-injection facilities, overdose-prevention programs, and referral to outpatient services. Indeed, MI can support IDU-IE in their efforts to remain compliant with IE therapy.

In conjunction with psychosocial interventions, the provision of pharmacotherapy for substance use disorders is a critical element of care for individuals who are receiving treatment for IDU-IE. There is a substantial body of evidence indicating the effectiveness of OAT in multiple domains for individuals with OUD, including reduced mortality, reduced morbidity, improved quality of life, reduced length of stay in hospital, and reductions in the use of illicit drugs [54,55]. OAT, including methadone and buprenorphine, should be instituted immediately upon admission for patients with endocarditis who inject opioids with careful attention to withdrawal signs and symptoms

[56–58]. In addition, OAT can be used for long-term treatment of OUD, which can be initiated in hospital [56].

For patients who only inject stimulants and not opioids, there are no approved pharmacotherapies for the treatment for stimulant use disorder in the absence of underlying ADHD [59,60]. Although patients with stimulant-related IDU-IE tend to have milder withdrawal than those who inject opioids, they should still be provided with primarily behavioural interventions. While there are many behavioural interventions for the treatment of substance use disorders, cognitive behavioural therapy (CBT) and Contingency Management (CM) are two of the most popular. A recent meta-analysis on the effectiveness of CBT for the treatment of stimulant use disorder found inconsistent evidence for its efficacy [61]. CM, however, is a more established, cost-effective, evidence-based behavioural intervention for the treatment of stimulant use disorder, where individuals are provided with reinforcers (such as vouchers, prizes, or medication 'carries') based on abstinence from drugs. Although CM is the most efficacious treatment for stimulant use disorders, widespread implementation can be challenging, as most hospitals and outpatient programs do not currently provide it [62].

Even in patients with the most severe forms of addiction, there is an abundance of literature demonstrating that the combination of MI and harm reduction approaches reduces the use of illicit substances, improves patient engagement, and reduces morbidity and mortality [54,55]. While the goal of abstinence is likely the best method for preventing reinfection in IDU-IE, treatment should always remain patient-centered, and often, harm-reduction is the bridge to future abstinence.

Practical strategies could address multiple domains. Regarding discharge planning, the growing utilization of inpatient addictions services has facilitated treatment on an outpatient basis, reducing the severity of the addiction [76]. Providing at-risk patients with take-home naloxone kits is another established harm-reduction strategy that can save lives, particularly when patients with prolonged hospital admissions who might have lost their tolerance for opioids [77]. Overdose-prevention sites, needle and syringe exchange programs, and safe injection facilities have been shown to reduce the incidence and transmission of HIV, and these benefits may transfer to IE [78].

In many ways, admission to hospital for surgical intervention in IDU-IE is an opportunity to connect patients with life-saving multidisciplinary treatment combining medical, surgical, psychiatric, and addictions care.

5. Ethical considerations in IDU-IE

As cardiac surgery and traditional psychiatric care are both limited and expensive resources, concerns have been raised in justifying their use in patients with high risk of IE recidivism [51]. While newer psychotherapies are cost-effective, time-limited, and can reduce substance use quickly, they are not readily available in all centres and often do not address the acuity of certain aspects of care in IDU-IE [58,59]. Thus, the degree of lasting benefit must be weighed against the surgical risk, and this often takes into account the patients' age at presentation, the personal and financial cost of providing only non-surgical treatment, the cost-benefit analysis vis-a-vis other resource-intensive specialties with limited prognoses, as well as stigma towards patients with a history of substance use [71].

In making ethical considerations with respect to surgical treatment, there is conflicting evidence from existing prognostic studies regarding the degree of benefit and risk. In two long-term follow-up studies, the mortality of patients with IDU-IE ranged between 45 and 60% over a mean follow-up period of 13 to 22 months, respectively [72,73]. However, recent studies demonstrated that the heightened mortality risk is more likely to be related to the risk of reinfection rather than to operative mortality [74,75]. The risk of post-operative mortality is highest between 3 and 6 months, with PWID having hazard ratios that are approximately 10-fold that of patients who do not inject drugs

during this period. However, before and after this 3 to 6 month period, the hazard ratios for death or reoperation are not statistically different [74].

Given these inconsistencies, offering higher risk repeat surgery for recidivistic infection in IDU-IE leads to potentially magnified ethical challenges, especially when there is an established correlation between reinfection and recidivism. As patients with IDU-IE tend to be younger, the cost of potential repeated hospitalizations for repeated infections as well as post-operative complications, such as congestive heart failure, arrhythmias, renal failure, must also be considered [60]. On the other hand, some patients who require multiple operative attempts enjoy excellent outcomes [70].

Miljeteig and colleagues, using an established model of impartial ethical analysis, looked at reoperation in IDU-IE and highlighted the unethicity of refusing life-saving treatment on the basis that disease recurrence is self-inflicted [71]. Although modifiable risk factors, such as obesity, smoking, inactivity, and alcohol use, have well-established impacts on the development of cancer and heart disease, we do not consider cancer to be a “self-inflicted” disease nor do we refer to heart disease as “behavioural” – yet, we commonly use these terms to unfairly chastise PWID. Furthermore, cost-benefit analysis and calculations of minimal survival duration are less commonly discussed in relation to the often-exorbitant costs of novel chemotherapies or certain cardiovascular procedures. Consequently, oncology frequently affords patients a comparable length of life benefit to cardiac surgery in IDU-IE with similar associated morbidity and mortality [71]. As well, critically ill cancer patients are frequently treated with prolonged mechanical ventilatory support, with < 50% weaning success [73].

Miljeteig and colleagues also drew parallels between alcohol-related liver transplantation and valvular-replacement in IDU-IE in terms of the finite financial and operational resources involved in both [74]. While the authors recognized that low likelihood of benefit from surgical intervention is a reasonable contraindication to proceeding with either treatment, the discussion of how to identify these circumstances was not within the scope of the article. Hence, ethically-informed decision making remains a key priority for clinicians who are expected to navigate complex medical scenarios, not unlike those encountered in IDU-IE [71].

6. Future directions

The management of IDU-IE is a challenging and controversial subject for which there is a limited evidence-base. A survey of attitudes and practice patterns that exists among surgeons and across institutions would be valuable. A qualitative study among patients with IDU-IE could serve to establish risk factors for recidivism and to identify patterns among IDU-IE patients with encouraging post-operative outcomes. Quantifying the effectiveness of harm reduction methods to prevent reinfection in IDU-IE would also address an established literature gap.

As the value of structured perioperative psychiatric care has become more evident, our institution has recently established an addictions medicine consult service, where we will be investigating the impact of this on both operative decision-making and surgical outcomes. Given the strong evidence-base for the cost-effectiveness of addictions treatment, surgical outcomes for IDU-IE may be improved by adding individualized addictions care for these vulnerable patients [20,44,58,80,81].

Finally, we believe there is a strong need for the development of a clear and structured multidisciplinary protocol for the management of infective endocarditis in PWID as well as expert consensus on surgical indications based on medical and psychiatric risk factors. The value of psychiatric and psychotherapeutic interventions, particularly addressing the traumatic-etiologicals, cannot be over emphasized. There remains a paucity of research quantifying the specific contributions of psychiatric or addictions interventions in the IDU-IE population. And

while there are two well-validated addiction severity assessment tools (the Addictions Severity Index [82] and the Maudsley Addiction Profile [83]), these are lengthy and cumbersome for application on a busy surgical service. Thus, a rapid screening tool to assess patient's motivation for change, incorporating principles of MI, harm-reduction, and psychiatric risk stratification, would be helpful in IDU-IE management and could be a potential topic of future research.

7. Conclusion

In the wake of the opioid epidemic, an increasing number of individuals have been affected by the sequelae of substance use disorders. Infective endocarditis in the setting of injection drug use (IDU-IE) is one of the most visible of these sequelae. IDU-IE is a severe infection that leads to significant morbidity and healthcare related costs, and rates of IDU-IE are increasing and will likely continue to do so without targeted interventions to help affected individuals. As such, cardiac surgery represents a high-intensity intervention with appreciable risk, and the benefit it is not always clear. As patients often present acutely, it is not feasible to use drug abstinence as a prerequisite to surgery. However, outcomes in those with IDU-IE can likely be improved by combining the medical and surgical treatment of the intra-cardiac infection with the psychiatric management of the underlying substance use disorder. Involvement of inpatient psychiatry and addictions teams can bridge IDU-IE patients with adequate outpatient treatment options for their underlying addiction, including focused pharmacotherapies and psychotherapies. Overall, the diagnosis and treatment of IDU-IE in hospital provides an opportunity for the delivery of addiction treatment, counseling, and other forms of harm reduction intervention.

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Conflicts of interest

The authors have no relevant conflicts of interest to report.

Appendix 1. Search strategy

- PubMed: inception to January 24, 2019
 - ((endocarditis) AND injection drug use) AND management/41 articles
- MEDLINE: inception to January 24, 2019
 - exp ENDOCARDITIS/27090
 - exp Substance Abuse, Intravenous/14345
 - exp DISEASE MANAGEMENT/61328
 - 1 and 2 and 3/1 articles
- CINAHL: inception to January 24, 2019
 - (MH “Endocarditis+”) OR (MH “Endocarditis, Bacterial”)/3296
 - (MH “Intravenous Drug Users”) OR (MH “Substance Abuse, Intravenous”) OR “intravenous drug use”/5876
 - (MH “Treatment Outcomes+”)/298,339
 - S1 AND S2 AND S3/20 articles
- Cochrane library: inception to January 24, 2019
 - MeSH descriptor: [Endocarditis] explode all trees/139
 - MeSH descriptor: [Therapeutics] explode all trees/281,626
 - MeSH descriptor: [Substance Abuse, Intravenous] explode all trees/378

- d. 1 and 2 and 3/4 articles
5. PsycINFO: inception to January 24, 2019
 - a. MeSH descriptor: [Heart Disorders] explode all trees/13534
 - b. MeSH descriptor: [Intravenous Drug Usage] explode all trees/3748
 - c. MeSH descriptor: [Treatment] explode all trees/724,393
 - d. 1 and 2 and 3/0
6. EMBASE: inception to January 24, 2019
 - a. MeSH descriptor: [Endocarditis] explode all trees/50,674
 - b. MeSH descriptor: [Intravenous Drug Abuse] explode all trees/10,057
 - c. MeSH descriptor: [Treatment Outcome] explode all trees/1,484,138
 - d. 1 and 2 and 3/101
 - e. Limits: English Language, Humans, EMBASE/93

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