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Infective endocarditis in intravenous drug users

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ABSTRACT

Since its first documented case in 1646, the epidemiology of endocarditis has significantly evolved. In the modern era, endocarditis has been increasingly associated with invasive procedures, medical devices, and intravenous drug use (IVDU). Patients at greatest risk include those with immunosuppression due to diabetes mellitus, human immunodeficiency virus (HIV), transplant medications, and increased survival of those with congenital heart or prosthetic heart valves. Prevalence of this disease has also significantly evolved due to technology in detection and prophylaxis. We aim to provide a comprehensive review of injection IVDU epidemiology, mechanism, medical and surgical treatment, ethical dilemmas involved in the treatment of this high-risk population, and future directions in the management of this lethal disease.

Introduction

Although the earliest autopsies of patients with endocarditis reported "round carbuncles" extending from the left ventricle [1,2], the term vegetations was coined due to the apparent similarity of the "excrescences" to syphilitic warts [3]. With invention of the stethoscope, clinicians of the 1800s had the ability to detect clinical abnormalities associated with endocarditis. Much of the anatomic vocabulary is attributed to Bouillard who recognized the association of "rheumatic fever" with endocarditis [4,5]. Osler went on to describe endocarditis as a "peculiar morbid process" characterized by contamination of blood, constitutional symptoms and emboli [4]. Now recognized as an inflammatory disorder of the inner layer of the heart, endocarditis can extend beyond valvular vegetations to invasion of chordae tendinae, sinuses of valsalva, the fibrous skeleton of the heart and the interventricular septum, with potential for systemic embolization, not sparing of coronary arteries (Fig. 1). Despite the availability of powerful antibiotics and advanced microbial culture and imaging techniques, infective endocarditis (IE) carries a high morbidity and mortality with rising prevalence, especially those who use intravenous drugs (IVDU) [6,7].

The number of endocarditis hospitalizations in the US have steadily increased from 0.32 to 0.75 cases per 100,000 hospitalizations over the past two decades [7]. Prior to the widespread use of antibiotics, IE was predominantly associated with rheumatic or congenital heart disease [8]. During this era, patients affected by IE are increasingly those with prosthetic heart valves, hemodialysis access, indwelling venous catheters, cardiac device implants including surgical and transcatheter valves, as well as immunosuppression [9–13].

IVDU comprises 8–37.8% of all modern cases of IE, with a rising incidence up to 56% of annual IE volume in a single tertiary center [14–18]. Among IVDU, the annual rate of bacterial endocarditis is approximately 1.5–20 per 100 addicts, nearly 20-fold higher rate than the general population [19–23]. The increase in IVDU-IE is concomitantly rising with the growing rate of heroin injection and opioid abuse, as well as the dramatic decrease in the prices of heroin and cocaine leading to increased frequency of use [24,25]. The 2014 National Survey of Drug Use and Health estimated that 4.3 million individuals were users of non-prescription opioids, which is an alarming statistic given that these persons are 40 times more likely than the general population to use heroin or other injection drugs [26,27]. Non-medical use of opioids not only increases the risk of heroin injection, but has also been associated with injection crushed pills [28,29].

Well recognized among reports of IVDU-IE is the right-sided predominance of affected valves. In non-IVDU-IE, only 10–13% of cases involve right-sided valves with the aortic being the most common [30,31]. In contrast, among IVDU-IE, 76% of cases

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Fig. 1. Pathologic examination of active infective endocarditis resulting in valvular vegetations (A), leaflet perforation(B) and coronary artery embolic occlusion(C, left circumflex coronary artery outlined by dashed circle with intraluminal embolus noted by red arrow). Images courtesy of Dr. Michael Fishbein, Chief of Autopsy, Cardiovascular & Pulmonary Pathology, Department of Pathology, David Geffen School of Medicine at UCLA, Los Angeles CA.

are right-sided [32,33], with 40–69% affected the tricuspid valve [20,34,35]. This right-sided predilection is in contrast to 20–30% of IVDU-IE affecting aortic and mitral valves, and 5–10% involving multiple valves [36]. The mechanism of this right-sided predilection is hypothesized to be related to injection practices and physiologic parameters without a unique pathophysiologically proven culprit [36]. The proposed mechanisms responsible for right sided IE in IVDU include:

(1) Direct mechanical damage due to impurities included with injected substance.
(2) High bacterial load from skin and needles inoculated into the venous side and right-sided circulation.
(3) IV drug associated vasospasm leading to intimal damage and thrombus formation, thus providing a nidus for bacterial aggregation.

Impurities in injected drugs, including talcum powder and other particulate matter, used to augment the weight of these agents, are delivered directly to the right-side of the heart [37]. Right-sided valves serve as the primary filters for these impurities. These fillers may induce direct injury to endocardium and lead to damage of the tricuspid valve through repetitive bombardment [32,37].

Although IV heroin injection comprises the greatest proportion of IE associated with injection drug use, other substances such as cocaine may cause direct vasospasm and associated injury to valvular intima, initiating a cycle of injury, local thrombus formation, and ultimately seeding by bacteria [32]. Furthermore, substance-induced pulmonary hypertension may lead to increased pressure gradients and turbulence, further contributing to right-sided valve dysfunction and valve-leaflet damage [38].

Others have proposed that the right-sided prevalence of IVDU-IE to be related to cooperation between valvular endothelium and bacteria, specifically for *S. aureus*, while others have observed IVDU-associated *Enterococcal* and *Serratia maracesens* for left-sided endocarditis [39,40]. Based on these observations, others have proposed that valvular and bacterial morphologic interactions may make an organism uniquely resistant or susceptible to hemodynamic variation, manifesting in deposition on right versus left sided valves [41]. However, the evidence supporting this theory is not robust and negated by the observed predominance of Staphylococcus aureus in non-IVDU left sided IE [33,42], an organism that is also the most common cause of IVDU right sided IE.

It is generally accepted that turbulent flow and the resulting endocardial injury can predispose valve surfaces to bacterial seeding. Patients with valvular heart abnormalities such as bicuspid aortic valve, mitral valve prolapse or any other acquired lesion causing stenosis or regurgitation, are at increased risk of endocarditis [43,44].

Organisms/epidemiology

The epidemiology of IE causative agents has also evolved over the past 30 years, with S*tapylcocci* and *Streptcocci* comprising 80% of IE cases at the present time [45]. Recent reports have shown *Staphycoccal* species account for up to 40% of IE cases, with *S. aureus as* the predominant species (25–30%) in nosocomial and non-nosocomial acquisition [45,46]. *Streptococcal* organisms contribute to an additional 30% of IE cases [45]. Of the *Streptococcal* group, 30% are associated with *viridans* group, while 20-to 50% are attributed to *S. gallolyticus*, a *Strep. bovis* group member [31,47]. *Enterococcal* and gram-negative IE, most commonly the HACEK group (*Haemophilus, Aggregatibacter, Cardiobacterium, and Eikenalla*) accounts for approximately 15% of IE cases. Fungal organisms are rare causative agents, with *Candida* species the most common causes of endocarditis among all other fungal agents. Additional fastidious organisms include *Coxiella burnetii, Bartonella* species, and *Trophyeryma Whipplei* [45].

Similar to non-IVDU IE, *S. aureus* is the organism most commonly implicated in IVDU IE (68% of IVDU, 28% of non-IVDU) [36]. This epidemiologic observation is not unexpected as intravenous drug users have been found to have higher rates of *S. aureus* skin colonization compared to peers using exclusively oral substances [48] as well as non-drug users [49,50]. Patients with IVDU may have damaged nasal mucosa and skin, facilitating colonization with *S. aureus*. Breaking of the skin barrier with a needle appears to provide a direct route to the bloodstream for skin organisms [51]. Beyond S. aureus, isolation of more rare microbiologic entities is also more prevalent for IVDU IE compared to their non-IVDU peers, with higher incidence of *Pseudomonal*, polymicrobial, and fungal disease [37]. Furthermore, use of saliva for injection substrate has been associated with culture of classically non-pathogenic organisms such as *Haemophilus parainfluenzae, Eikenalla corrodens*, and *Streptococcus milleri* [52]. Taken together, the microbiologic differences between IVDU and non-IVDU IE are expected given the higher likelihood of poor skin hygiene and sterilization at injection.

Additional pathophysiologic explanations for *S. aureus* predominance in IVDU IE include organism-specific characteristics such as expression proteins that enable it to adhere particularly well to host tissue, to diminish immunoglobulin phagocytic capability, and to activate extrinsic clotting cascade upon phagocytosis that is essential to thrombus and vegetation formation [53]. *S. aureus* predilection for right-sided valves in IVDU IE has also been proposed to be related to greater expression of matrix molecules that bind to microbial surface components recognizing adhesive matrix molecules (MSCRAMM) which allow for host colonization [54]. Studies have suggested that MSCRAMM expression is greater on right-sided valvular structures in IVDU patients, predisposing to *S. aureus* adherence even with minimal endothelial damage.

Diagnosis

The diagnosis of endocarditis is a multimodal one, and requires expertise from several specialists [37]. Among the IVDU population, presence of fever should serve as a low threshold for consideration and evaluation of infective endocarditis [37]. Clinical suspicion, a myriad of signs of symptoms as well as imaging are needed to establish this diagnosis. The value of echocardiography, in particular transesophageal, cannot be over emphasized given the variability of physical manifestations, especially of right-sided endocarditis, as tricuspid murmurs are difficult to detect and other classics signs such as Osler nodes, splinter hemorrhages, Roth spots, and heart failure are exceedingly rare [55]. Although septic pulmonary emboli are present in 80% of patients with right-sided IE, presentation with pulmonary symptoms occurs in less than 20% of patients [56].

Transthoracic echocardiography (TTE) is more sensitive in detection of native valve IE, with greater than >90% sensitivity, compared to bioprosthetic and mechanical ones [57]. Imaging of the valve, principally performed via TTE, can also be used to determine the extent of annular destruction and fistulization as well as predict the extent of required surgical reconstruction. Transesophageal echocardiography (TEE) has not been shown to significantly change management of native valve endocarditis that is diagnosed with TTE and clinical manifestations. Thus, TEE is recommended when TTE is nondiagnostic or when intracardiac device leads are present.

Limitations of echocardiography include inability to distinguish vegetation from thrombus, or infected versus non-infected vegetation. Furthermore, echocardiography has variable sensitivity for periannular disease in the setting of prosthetic valve endocarditis. Thus alternative imaging modalities are gaining interest [58]. Positron-emission tomography- computed tomography (PET-CT) using ^{18}F-fluorodeoxyglucose may be an additional diagnostic modality when echocardiographic findings are inconclusive or in patients with prosthetic cardiac devices [59]. PET-CT also aides in the identification of embolic foci in most tissues, except for brain and kidneys, where physiologic 18F-FDG uptake is high at baseline. Antimicrobial treatment and recent cardiac surgery are additional factors that impact the sensitivity and specificity of tracer uptake. In contrast, limited evidence exists for the use of leukocyte-radiolabeled studies in the diagnosis of IE with reported sensitivity of 64%, but specificity of 100% with technetium-99 m [60].

Similar to echocardiography, cardiac CT-angiography (CCTA) provides important valvular anatomic and mechanical information. Cardiac-gated imaging allows for "motion-free" imaging, but may also limit its diagnostic sensitivity if the abnormality of interest is reconstructed only in diastole or systole. Compared to TEE, CCTA is superior in recognizing aortic perivalvular pseudoaneurysm [61,62], with reports of 100% sensitivity and specificity as the size of the vegetations increases (>10 mm) [61] while it has been found to miss leaflet perforations and vegetations ≤4 mm [62]. An additional benefit of endocarditis diagnosis with CCTA is noninvasive assessment of coronary anatomy and atherosclerotic burden [62,63].

Magnetic resonance imaging (MRI) is increasingly utilized to diagnose valvular and nonvalvular vegetations, as well complications of endocarditis such as perivalvular abscess, pseudoaneurysms, and fistulae [58,64]. Limited analyses of MRI utility in IE diagnosis have proposed the association of delayed MRI contrast enhancement with endothelial inflammation prior to manifestations of peri–valuvlar extension [65]. Gadolinium enhanced Cardiac MRI allows visualization of endocardial fibrotic changes induced by IE. While PET-CT has relatively low sensitivity for detection of emboli in hypermetabolic organs such as the brain and kidney, MRI is superior for investigation of cerebral and abdominal emboli. In an isolated study, the utilization of brain and abdominal MRI resulted in definite or possible recognition of endocarditis in 28% of nondefinite IE [65].

Despite evolution of these adjunctive imaging modalities, European and American guidelines have been slow to integrate multimodal imaging, largely due to insufficient evidence and debate on appropriate indications as well as variable sensitivity and specificity [64]. The European guidelines from 2015 purport that multimodal imaging should not serve as a replacement for TEE, but rather as an additional tool in establishing a diagnosis that is "possible" or "rejected" by Duke criteria when clinical suspicion remains high [66]. In summary, multi-modal imaging has been shown to yield greater diagnostic clarity in patients with prosthetic valvular endocarditis.

Surgical therapy

Despite optimization of medical therapy, up to 50% of patients with IE will ultimately require operative intervention [67]. Early engagement of a multidisciplinary team consisting of a cardiologist, infectious disease physician, neurologist and a cardiac surgeon are recommended. In a study by Chirillo et al., implementation of a multidisciplinary team approach towards the treatment of patients with IE resulted in a shorter time to operative intervention, and a concomitant reduction in short term and 3-year mortality [68].

There are three main indications for surgical intervention in the patient with IE [66,69]:

(1) Heart failure
(2) Embolic complications
(3) Persistent bacteremia.

Heart failure is the most frequent complication of IE and is the most common indication for surgical intervention [8]. Heart failure may present as cardiogenic shock from severe regurgitation secondary to valve leaflet perforation, ruptured chords, or from lack of leaflet coaptation due to vegetations.

The next most common indication for surgical intervention is the presence of vegetations. The risk of embolization in the setting of native valve endocarditis is 13–44% among patients with IE. Risk factors for embolization include left- sided vegetation size >10 mm, vegetation mobility, vegetation location on the anterior mitral leaflet, prior embolization, and infection with *S. aureus*, Streptococcus bovis, or fungus [70]. Clearly, right sided vegetations may be treated more conservatively with a lower risk for embolization. Other reasons for surgical treatment of endocarditis include annular destruction which can ultimately lead to pseudoaneurysm formation.

Surgical treatment should be considered once antibiotics have failed to clear systemic infection or if any of the above indications are met. Once a patient has been identified as having a surgical indication for intervention, the next question relates to timing. Patient with cardiogenic shock from heart failure require urgent operative intervention, despite the increased perioperative risk. Early surgery, defined as surgery at index hospitalization, for native valve endocarditis is associated with an in-hospital mortality benefit compared with medical therapy alone [71]. This is especially true to aid in the prevention of embolic disease as risk of embolic stroke is highest [72,73]. Many patients undergo intervention to reduce risk of embolic stroke or to prevent repeat embolic stroke. Early surgery has been shown to reduce systemic embolic events in IE [74]. One of the concerns of operative interventions in patients with recent embolic stroke is the conversion to hemorrhagic stroke during full heparinization required for cardiopulmonary bypass. Because of this, many surgeons would wait up to one month after an embolic stroke before surgery. However, new data suggests that early intervention may be safe in select patients.

Using propensity score matching, Samura et al. performed a retrospective review of 45 patients who underwent early, within 3 days of documented stroke, or late, after three days, who had surgery for infective endocarditis [75]. They found improved clinical results in patients with a cerebral infarction less than 2 cm who underwent early operative intervention compared to those that had intervention after three days from their stroke [75]. Therefore, all patients considered for operations to treat IE should have thorough neurological evaluation and risk stratification prior to surgery.

Another argument against early surgery is the concern for the high local and systemic bacterial load that might result in the inoculation of the newly implanted surgical valve or suture material. Depending on the center's experience, surgeons may opt to intervene early in the cases of true early endocarditis, i.e., within three days of noting constitutional symptoms. Nonetheless, infection of a newly implanted valve for IE carries tremendous morbidity and risk of death.

Repair/replacement/valve type

The principle dogma in surgical intervention for IE is to remove all infected tissue. Right-sided IE is less common, and responsible for only 5–10% of all IE cases [31,66]. Of these, more than 90% involve only the tricuspid valve [31]. A major risk factor for tricuspid valve IE is IVDU, accounting for 30–40% of such cases [14,66]. Other sources of right sided IE include, hemodialysis lines, pacemaker leads, and PICC lines. In patients with right sided IE, repair is preferred and often feasible. There are numerous techniques described for repair of the tricuspid valve which include, pericardial patch repair of perforated/excised leaflets, annuloplasty with suture or bands, bicuspidization or placement of neochords [76,77]. Valves that are not amenable to repair are often replaced with a bioprosthetic valve. This avoids the need for long-term anticoagulation and issues with noncompliance, especially in a population with poor adherence such as in intravenous drug abusers. Occasionally, excision of the leaflets, leaving the valve fully incompetent can be performed leaving the patient with severe tricuspid regurgitation [78]. However, this technique is used infrequently and reserved for young patients who are likely to relapse into IVDU and re-infect the valve.

For left sided reconstructions, options include mechanical or bioprosthetic valve replacement, homografts, or the Ross procedure. Some authors advocate the use of aortic homograft given the nature of the infected field. A benefit of homograft is the low risk of relapsing infection but at a trade-off with high rates of structural valve degeneration and the need for operative re-intervention in 15% of cases at 10 years and up to 53% at 15 years [79]. In regards to mechanical versus bioprosthetic valve for replacement, the current consensus is that either valve is appropriate. In a recent database examination of over three thousand patients by Toyoda et al. [80], the authors demonstrated a similar survival and freedom from endocarditis recurrence between bioprosthetic and mechanical valves. An important consideration during implantation of a bioprosthetic valve would be to ensure that at least a 21 mm valve can be implanted. One of the pitfalls of bioprosthetic valves is structural valve degeneration, up to 63% at 10 years [81]. By implanting a larger valve at the index operation, the patient would have the option of valve in valve transcatheter aortic valve implantation for the treatment of structural valve degeneration.

In severe cases of IE with invasion of the annulus or the aortomitral curtain, extensive reconstruction using autologous or bovine pericardium is required to recreate a suitable plane for valve seating and exclusion of abscess cavities. Use of prosthetic material including felt should be minimized if possible, to reduce the risk of relapse.

Regardless of technique of surgical intervention, several studies have shown that surgeons are less likely to operate on patients with IVDU-IE because of concern for recurrence and reinfection of prosthetic valves, which is associated with significantly higher operative risk upon reintervention and lower likelihood of medical cure [82]. The observed reluctance at intervention for IVDU-IE is reflected in stable rates of valve replacement since 2007 despite the perpetual increase in the prevalence of IVDU-IE [7].

Antibiotic therapy

Antibiotic treatment of IE remains an important adjunct to surgical management and may be used as the sole therapeutic modality in select cases. Typical guidelines for antibiotic therapy recommend 6 weeks of antibiotics targeted towards the organism recovered from the bloodstream. Empiric treatment should include coverage against staphylococcal and streptococcal species as well as enterococcus faecalis. Patients with uncomplicated right sided IE may be candidates for an abbreviated treatment with either oral or intravenous antibiotics. Those with renal failure, disseminated infection or inability to defervesce within 48 h of antibiotic treatment are not considered low risk and warrant a full course [83].

Several previous studies have examined the efficacy of an abbreviated antibiotic course in IVDU-IE with *S. aureus* and have found mixed results [84–86]. In several studies of right-sided IVDU-IE, two week courses of IV antibiotics achieved 93–94% cure rate [87,88]. Another prospective randomized trial of right-sided IVDU-IE showed comparable results for patients treated with parenteral antibiotics and those who received ciprofloxacin and rifampin [89]. A recent randomized multi-center trial from Denmark, demonstrated that for left-sided endocarditis, oral antibiotics treatment after an initial 10 days of IV antibiotics using the composite primary outcome of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse of bacteremia within 6 months of treatment completion, was non-inferior [90]. An important limitation of this study was absence of MRSA cases. Although, abbreviated postoperative antibiotics duration has also garnered increasing interest over the last three decades [91,92], dedicated and contemporary study of these antibiotic practices among IVDU-IE patients is warranted.

Several concerns specific to the IVDU population add to the complexity of antibiotic therapy in this group. Fear of catheter manipulation and use for illicit drug delivery greatly limit the outpatient utility of peripherally inserted central venous catheters (PICC) in this cohort. Moreover, unreliable follow up and outpatient monitoring make traditional oral antibiotic therapy unreliable in unsupervised settings. In light of such limitations, oral unsupervised antibiotic therapy in IVDU-IE cannot be recommended.

Novel long-acting antimicrobials, such as dalbavincin or oritavancin, have been proposed as alternative agents that mitigate the risks associated with outpatient intravenous and unsupervised traditional oral regimens [93]. Although clinical trial data are lacking, retrospective and observational studies have demonstrated efficacy in invasive gram-positive infections, with one small case series reporting an endocarditis cure rate of 92.4% after treatment with conventional antibiotics [94]. With the half-life of these lipoglycopeptides ranging from 147 to 393 h, treatment adherence is nearly inherent to administration [95]. Further investigation of these long-acting agents are warranted given a number of case-reports that repot incomplete treatment and induced resistance [93,96].

Outcomes

Compared to others cases of endocarditis, IVDU-IE is associated with 70% longer length of stay, and nearly twice the costs for in-

dex hospitalization [97]. Observational studies of in-hospital mortality for IVDU-IE patients have shown either similar or lower rate of mortality compared to non-IVDU counterparts [16,17,82]. These findings are likely a reflection of the younger age of IVDU-IE population and lower burden of other comorbidities as well the frequent right-sided nature of disease those with IVDU [82]. In contrast, IVDU-IE patients have higher rates of readmission and recurrent infective-endocarditis after the initial episode [98,99]. However, compared to non-IVDU IE peers, IVDU patients had a 10-fold higher hazard of death or reoperation between postoperative days 90 and 180 [14].

More recently, readmission within 90 days has been reported between 22 and 49% [16,97,100], with 28% of patients using injection drugs again at readmission [100]. In one institutional study, more than half of discharges lacked documentation of any discussion regarding addiction treatment, with only a minority of patients offered treatment by a social worker or evaluated by psychiatry [97]. Given the high rates of relapse observed with behavioral- or medication-only interventions, medication associated treatment (MAT), defined as "the use of medications, in combination with counseling and behavioral therapies to provide a whole patient approach to the treatment of substance use disorders", has been increasingly studied as a comprehensive modality to combat the rising incidence and prevalence of opioid abuse [101–103]. A review of the health-care expenditures of Medicaid enrollees in Vermont with opioid addiction or dependency revealed that patients enrolled in MAT had lower rates of rehospitalization, emergency department visits, and overall health care utilization, offsetting the costs of MAT [104]. Although evidence on MAT impact on criminal behavior, risk factors of HIV and hepatitis C virus (HCV) remains ambivalent, MAT has been shown to decrease overall mortality, and improved treatment adherence after release from prison [105–108]. With average wait times for MAT up to two years in certain rural regions of the US, additional resources and funding are warranted to address these deficiencies of care [109].

Given the significant readmission and recurrence burden, several groups have debated the ethical obligation to allocate resources to management of patients with high rates of recurrence [110,111]. Physicians are faced with conflicting ethical and moral quandaries of providing life-saving definitive interventions, while also serving as responsible stewards of healthcare resources. As reoperative valve operations for IVDU-IE have double the mortality of first time interventions [112], how does a surgeon justify use of these resources that have low likelihood of yielding success? How many operations are performed before surgical intervention is deemed futile? If a patient was never offered the resources for management of his substance abuse, is it just to withhold repeat intervention? The notion of a contract between a patient and surgeon preoperatively has also been debated [113,114].

Perhaps the focus of resource utilization should shift from whether surgical therapy should be offered, to aggressive and progressive management of IVDU addiction. With estimated costs of greater than $300,000 for patients with recurrent hospitalizations for endocarditis, transfer to residential addiction treatment has been associated with 2.43 million dollars in costs savings over 6 years for the Virginia Commonwealth University Health System [115]. Investigation of oral antibiotic management of endocarditis may also decrease the potential for contamination and recurrence if long-term intravenous access is no longer required [90]. Thus, the rising rates of IVDU-IE represent an important opportunity for intervention in order to prevent patients from the most common and ultimate consequence of IVDU, overdose and mortality [97].

The physiologic, surgical and psychosocial complexity of IVDU-IE requires the expertise of a multi-disciplinary team to personalize interventions at each stage of a patient's hospitalization. Inclusion of marginalized IVDU patients in prospective randomized trials will remain a challenge. Creative and ethical study design will be needed to investigate medication and psychosocial interventions with justifiable resource investment to address the high morbidity and mortality associated with IVDU-recidivism. National and international leaders of cardiovascular societies must lead the way in maturing multi-disciplinary teams that will establish more standardized protocols in ensuring that patients undergoing treatment for IVDU-IE have been offered the medical and psychiatric therapy necessary to overcome physiologic dependence. The question of inpatient versus outpatient rehab and timing of initiation remains unknown and also warrants further investigation.

In summary, IVDU-IE is a rising entity and requires multidisciplinary longitudinal rather than episodic management. Antibiotic treatment tailored to the cultured organism is the cornerstone of therapy for all IE. A combination of clinical, echocardiographic and microbiologic data are required to reach this diagnosis. Surgical therapy appears to be more efficacious in early endocarditis while a variety of methods are used to eradicate intra-cardiac infection. Future efforts should look beyond acute hospitalization and focus on drug rehabilitation and provision of medical and social resources to reduce relapse and improve the poor long-term outcomes associated with IVDU-IE.

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