Management of Infective Endocarditis in Addicts

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Abstract

Infective endocarditis is responsible for 5% to 8% of hospital admissions among injection drug users, and the overall incidence of infective endocarditis in this population is estimated to be 1 to 20 cases per 10,000 injection drug users per year. Whether this increased risk is caused by systemic or immunosuppressive effects of cocaine or by injection habits (more frequent injection or needle sharing) is currently unknown. Injection drug users with underlying HIV infection seem to be at an increased risk for infective endocarditis.

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Introduction:

Injection drug use is a well-recognized and common predisposing condition of infective endocarditis (IE), a life-threatening syndrome. To the best of our knowledge, IE accounts for 2–5% per year among the intravenous drug users (IDUs). Approximately 41% of IDUs with bacteremia will develop IE **(1)**.

Injection drug use (IDU) is a symptom of both severe untreated opioid use disorder and other substance use disorders and has been a key criterion in the clinical definition of IE **(2)**.

The impact of IE on injection drug users (IDUs) in terms of individual health and psychosocial well-being can be devastating, especially considering that it affects an overall younger and otherwise largely healthy patient population. Despite imaging and surgical advancements in the field of IE, there have been limited focus and research on the prevention and management of IE in IDUs**(3)**.

In response, many institutions have developed endocarditis teams, groups of multispecialty clinicians with expertise in IE and addiction consultation, and have improved patient outcomes **(4).**

Addiction medicine

Addiction treatment has long been siloed from mainstream medical care, causing long-standing disparities in access to treatment for substance use disorders, particularly opioid use disorder **(5).**

As a consequence, the United States experienced >100 000 drug overdose deaths and outbreaks of HIV and hepatitis C infections in 2021 in networks of IDUs, as well as increasing numbers of IDUs with IE and other severe invasive bacterial infections related to injection drug use **(6).**

Treating IE alone without concomitant addiction treatment for substance use disorder is failing to treat the underlying cause of illness, an ideal that is a principal tenet in all other medical conditions. We have considerable evidence that supports the integration of addiction treatment into the care of hospitalized individuals with injection drug use–related infections, including IE**(7).**

- **Diagnosis of Substance Use Disorder in a Patient with IE Related to Injection Drug Use**

Evaluations that are limited to asking patients "do you use drugs or alcohol?" are not sufficient. Further evaluation for substance use disorder in IDUs with IE includes obtaining a history of present or past substance use, including quantity and routes;

determining risk for substance withdrawal; asking about previous addiction treatment experience and response; and obtaining history of overdose and injection-related complications such as, but not limited to, history of IE, prior episodes of skin and soft tissue infections, musculoskeletal infections, hepatitis C, and HIV infections **(8)**.

Substance use disorder is diagnosed from 11 criteriadescribed in the**Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, text revision "DSM-5-TR"**in which the presence of 2 to 3 criteria indicates a mild substance use disorder; 4 to 5 criteria, moderate substance use disorder; and ≥6 criteria, severe substance use disorder. Substance use disorder is named by the substance involved in the disorder such as opioid, alcohol, tobacco and cannabis **(9).**

Key elements of the physical examination of IDUs include a skin examination (to evaluate previous and current injection sites for inflammation, induration, and scarring), evaluation for cirrhosis, evaluation of oral health, and assessment of substance withdrawal. Stimulant withdrawal generally involves hypersomnia described as "crashing," anxiety, irritability, anhedonia, poor attention, and craving. In particular, opioid withdrawal syndrome is an extremely uncomfortable syndrome involving mydriasis, rhinorrhea, diaphoresis, diffuse myalgias, gastrointestinal upset, yawning, prominent anxiety, and irritability**(10).**

DSM-5-TR Substance Use Disorder Criteria(9)

1. Taking the substance in larger amounts or for longer than you're meant to
2. Wanting to cut down or stop using the substance but not managing to
3. Spending a lot of time getting, using, or recovering from use of the substance
4. Cravings and urges to use the substance
5. Not managing to do what you should at work, home, or school because of substance use.
6. Continuing to use, even when it causes problems in relationships.
7. Giving up important social, occupational, or recreational activities because of substance use.
8. Using substances again and again, even when it puts you in danger.
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance.
10. Needing more of the substance to get the effect you want (tolerance).
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance.

The severity of opioid withdrawal can be measured with the Clinical Opiate Withdrawal Scale (COWS)**(Table 1)**which is a clinician-administered, pen and paper instrument that rates eleven common opiate withdrawal signs or symptoms. Generally, 0 is considered to be no symptom shown and 4 or 5 is considered to be the most common and severe symptom. The summed score of the eleven items can beused to assess a patient's level of opiate withdrawal and to make inferences about their level of physical dependence on opioids.The results are grouped into 3 categories of mild, moderately severe and severe. Mild consists of 5 to 12 points, moderately severe consists of 13 to 24 points and anything above 36 points is severe and requires direct medical attention **(11).**

Table (1): Clinical Opiate Withdrawal Scale (COWS) ***(11)***

Pulse rate: (beats/minute) Measured after patient is sitting or lying for one minute. 0-Pulse rate ≤ 80 1-Pulse 81-100 2-Pulse 101-120 4-Pulse ≥120	**Gastro-intestinal (GI) symptoms:**Over the last half an hour. 0-No GI symptoms 1-Stomach cramps 2-Nausea or loose stool 3-Vomiting or diarrhea 5-Multiple episodes of diarrhea or vomiting
Sweating: Over past half-hour not accounted for by	**Tremor:** Observation of outstretched hands.

room temperature or patient activity. 0-No report of chills or flushing 1-Subjective report of chills or flushing 2-Flushed or observable moistness on face 3-Beads of sweat on brow or face 4-Sweat streaming off face	 0-No tremor 1-Tremor can be felt, but not observed 2-Slight tremor observed 4-Gross tremor or muscle twitching
Restlessness: Observation during assessment 0-Able to sit still 1-Reports difficulty sitting still, but is able to do so 3-Frequent shifting or extraneous movements of legs/arms 5-Unable to sit still for more than a few seconds	**Yawning:**Observation during assessment 0-No yawning 1-Yawning once or twice during assessment 2-Yawning three or more times during assessment 4-Yawning several times/minute
Pupil size: **0-Pupils pinned or normal size for room light** 1-Pupils possibly larger than normal for room light 2-Pupils moderately dilated 5-Pupils so dilated that only the rim of the iris is visible	**Anxiety or irritability:** 0-None 1-Patient reports increasing irritability or anxiousness 2-Patient obviously irritable or anxious 4-Patient so irritable or anxious that participation in the assessment is difficult
Bone or joint aches: If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored. 0-Not present 1-Mild diffuse discomfort 2-Patient reports severe diffuse aching of joints/muscles 4-Patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin:** 0-Skin is smooth 3-Piloerection of skin can be felt or hairs standing up on arms 5-Prominent piloerection
Runny nose or tearing: Not accounted by cold symptoms or allergies. 0-Not present 1-Nasal stuffiness or unusually moist eyes 2-Nose running or tearing 4-Nose constantly running or tears streaming down cheeks	**Total score:** The total score is the sum of all 11 items. **5-12: mild** **13-24: moderate** **25-36: moderately severe** **≥ 36: severe withdrawal symptoms**

Urine testing can also be helpful in the evaluation of patients with substance use disorder but may be obtained in a non-punitive manner to promote wholistic medical care as an objective measure to confirm a substance use disorder diagnosis and to inform discussions with patients about infectious and overdose risks. Any evaluation of substance use disorder must be mindful of using non-stigmatizing, non-judgmental language that recognizes substance use disorder as a medical illness and values patients' dignity ***(12).***

- ***Comprehensive care to hospitalized patients with injection drug use–related IE***

Although not all patients with injection drug use–related IE have opioid use disorder, for those who do, the best practice would be to offer US Food and Drug Administration–approved medications (specifically buprenorphine or methadone) as soon as possible after the patient presents to the hospital**(Table 2)**. Both of these drugs treat opioid withdrawal and opioid cravings, reduce the risk of a patient leaving the hospital by patient-directed discharge and reduce all-cause mortality by >50%; they also facilitate effective management of acute pain ***(13).***

Patients may have other substance use disorders that do not have effective medication treatment options, or individuals may not currently desire treatment for substance use disorder. Health care teams may consider having open, nonjudgmental conversations with patients that

explore substance use disorders and injection drug use as complex behaviors with multiple opportunities to improve safety and to reduce harm.

When medications for opioid use disorder have been started in the inpatient setting, efforts may be made to ensure continuation of care after discharge ***(8).***

Table (2):Medications for opioid use disorder***(13)***

	Methadone	Buprenorphine	Extended-release naltrexone
Mechanism of action	Full opioid agonist	Partial opioid agonist	Opioid antagonist
Treats pain	Yes	Yes	No
Treats opioid withdrawal	Yes	Yes	No
Reduces opioid cravings	Yes	Yes	May be in some patients
Drug interactions	Significant, cytochrome P450	Not significant	Opioid medications
QTc prolongation	Yes	No	No
Starting dose	10 to 30 mg first dose, no more than 40 mg on the first day	2 – 4 mg	380 mg I.M monthly after 7–10 days without opioids
Reduces all-cause mortality	Yes	Yes	Insufficient data

- ***Appropriate response to patients who may have had return to substance use after a previous episode of IE***

Some patients will return to substance use after an episode of injection drug use–related IE. Moving toward an institutional culture that provides effective medication treatments, incorporates harm reduction principles, and provides nonjudgmental psychosocial support is essential to improving outcomes. For patients who return to use after treatment for injection drug use–related IE, it may be reasonable to offer re-entry into addiction treatment with medication and other recovery supports such as harm reduction. Patients who remain engaged in addiction treatment have the best outcomes after treatment for injection drug use–related IE ***(14).***

❖ Diagnosis of IDU-IE

Well recognized among reports of IDU-IE is the right-sided predominance of affected valves. This right-sided predilection is in contrast to 20–30% of IDU-IE affecting aortic and mitral valves, and 5–10% involving multiple valves.In case of the right-sided IE, the distribution of the valves involved is estimated to be as follows: tricuspid valve (90%), pulmonary valve (5%), and Eustachian valve (3%)***(15)***.

The mechanism of this right-sided predilection is hypothesized to be related to injection practices and physiologic parameters without a unique patho-physiologically proven culprit. The proposed mechanisms responsible for right sided IE in IDUs include:

A. Direct mechanical damage due to impurities included with injected substance.

B. High bacterial load from skin and needles inoculated into the venous side and right-sided circulation.

C. IV drug associated vasospasm leading to intimal damage and thrombus formation, thus providing a nidus for bacterial aggregation ***(15)***.

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. 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 ***(16)***.

The tricuspid valve may be more susceptible to heroin use, as heroin can cause an increase in pulmonary arterial pressure, creating more turbulence at the tricuspid valve. Substances such as

cocaine and metamphetamines, on the other hand, increase systemic afterload, causing increased turbulence at the sites of the aortic and mitral valves. Therefore, any shifts in the incidence of right versus left-sided IE may reflect the availability of certain illicit substances ***(17)***.

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***(18)***.

Some recent case reports have described the incidence of left-sided IE in IDUs without involvement of right heart valves, this could be explained by hematogenous spread of bacteria. One case report described an unusual case of an IDU patient developing acute decompensated heart failure following acute aortic regurgitation from IE without fever and right-sided heart or tricuspid valve involvement ***(19)***. Another one showed a classic presentation of fever and vascular phenomena with aortic valve vegetation in IDU patient ***(20)***. Also, a case of isolated mitral valve endocarditis in IDU patient was described and was found to be associated with patent foramen ovale (PFO)***(21).***

History and classic Oslerian manifestations (persistent bacteremia or fungemia, active valvulitis, immunological vascular phenomena, and peripheral emboli) help with a straightforward diagnosis in IE. Persistent fever and bacteremia are common manifestations of tricuspid valve IE. Typical clinical manifestations of IE comprise fever, positive blood cultures, and valvularvegetations on echocardiography. IE should be suspected in the presence of fever and embolic phenomena. ***(22)***.

Clinical manifestations are usually limited in the early IE of IDUs, right-sided endocarditis and S. aureus. Right-sided IE mainly present fever, cough, hemoptysis, dyspnea caused by pulmonary emboli, anemia, and no systemic emboli. Persistent fever associated with pulmonary events, anemia, and microscopic hematuria, the so-called "tricuspid syndrome," is the sign of clinical alert for tricuspid valve IE. Characteristically, right-sided IE does not develop immunological vascular phenomena (splinter hemorrhages, Roth spots, and glomerulonephritis) and the peripheral emboli. Right-sided and pacemaker wires IE can be associated with septic pulmonary emboli. The pulmonary embolism (PE) can induce pulmonary infarction, abscesses, pneumothoraxes, and purulent pulmonary effusions ***(3)***.

Usually, the association of clinical findings, positive blood cultures, and positive echocardiography (modified Duke criteria) set up the diagnosis. Only that, these modified Duke criteria have poorer diagnostic precision in the early diagnosis of IE from IDUs, which present fewer typical clinical manifestations, especially in those infected with S. aureus and HACEK. The addition of imagistic techniques cardiac/whole-body CT scan, cerebral MRI, ^{18}F-FDG PET/CT, and radio-labelled leucocyte SPECT/CT may increase accuracy of the modified Duke criteria in IDUs***(22)***.

❖ Antimicrobial therapy

According to current evidence, IE among IDUs presents a large spectrum of microbial pathogens. The most common etiology of right-sided IE in IDUs is Staphylococcus aureus (S. aureus) in about 75% followed by streptococci, Gram-negative bacilli, and fungi ***(3)***.

The incidence of negative blood cultures is reported as 2.5–31% and is associated with delayed diagnosis and treatment, with large vegetations, and with highest morbidity and mortality ***(22)***.

Polymicrobial endocarditis is characteristically for IDUs and may involve microorganisms such as Bartonella spp., Candida spp., or Tropherymawhipplei. The presence of E. corrodens should aware the likelihood of polymicrobial IE with embolic complications and relapses. In fact, there is a synergism between streptococci and E. corrodens***(23)***.

The choice of empiric antimicrobial therapy depends on the suspected microorganism, type of drug and solvent used by the addict and the infection location. In any case, S. aureus must always be covered. Initial treatment includes penicillinase-resistant penicillins, vancomycin or daptomycin, depending on the local prevalence of MRSA, in combination with gentamicin. If the patient is a pentazocine addict, an anti-pseudomonas agent

should be added. If an IVDA uses brown heroin dissolved in lemon juice, Candida spp. (not Candida albicans) should be considered and antifungal treatment added. Once the causative organisms have been isolated, therapy has to be adjusted ***(24)***.

Two-week treatment with oxacillin (or cloxacillin) without gentamicin is effective for most patients with isolated tricuspid IE if all the following criteria are fulfilled: MSSA, good response to treatment, absence of metastatic sites of infection or empyema, Absence of cardiac andextracardiac complications, absence of associated prosthetic valve or left-sided valve infection, < 20 mm vegetation, and absence of severe immunosuppression (<200 CD4 cells/mL)with or without acquired immune deficiency syndrome (AIDS)***(22)***.

Because of limited bactericidal activity, poor penetration into vegetations and increased drug clearance in IDUs, glycopeptides (vancomycin) should not be used in a 2-week treatment. The standard 4–6-week regimen must be used in the following situations: slow clinical or microbiological response (> 96 h) to antibiotic therapy, right-sided IE complicated by right HF, vegetations> 20 mm, acute respiratory failure, septic metastatic foci outside the lungs (including empyema) or extracardiac complications, e.g., acute renal failure, therapy with antibiotics other than penicillinase-resistant penicillins, IDUs with severe immunosuppression (CD4 count <200 cells/mL) with or without AIDS, or associated left-sided IE ***(22)***.

Because S. aureus accounts for the bulk (≈75%) of right-sided IE cases in IDUs and is the predominant (≈46%) pathogen in left-sided IE cases, we focus on IE caused by S. aureus***(25).***

- ***In-hospital antimicrobial management of IE attributable to S. aureus in IDUs***

The standard of care of IE attributable to S. aureus has included 6 weeks of intravenous antibiotics. It is believed it would be reasonable to offer this program to all IDUs with injection drug use–related IE. However, it is recognized that 6 weeks of intravenous antibiotics is often not feasible for all IDUs and that there is growing evidence that partial intravenous therapy followed by oral antibiotic treatment to complete a total of 6 weeks is a possible option***(26).***

A 2-week regimen is listed as a treatment option for uncomplicated right-sided IE attributable to methicillin-susceptible S. aureus and has been addressed in the 2015 AHA IE statement. However, it is not advocated for the routine use of this abbreviated regimen -which has previously been supported for use in select cases of uncomplicated right-sided IE- because of the lack of contemporary high-quality clinical trial data ***(8).***

- ***Discharge of IDUs with IE on outpatient parenteral antibiotic therapy (OPAT)***

Some IDUs can be discharged safely with intravenous antibiotics and a peripherally inserted central catheter. The Infectious Diseases Society of America and the AHA provide guidance for decisions on transitioning to outpatient parenteral antimicrobial therapy (OPAT) ***(27).***

Recently described integrated transitional care models present potential alternatives to prolonged hospitalizations to complete intravenous antibiotics, including residential addiction treatment programs willing to accept patients receiving OPAT, medical respite, and OPAT integrated with opioid use disorder treatment***(28).***

Critical elements of these models include multidisciplinary care involving infectious diseases, addiction medicine, or addiction psychiatry; initiation of medications for opioid use disorder; and linkage to continued care and case management, with an overarching focus on harm reduction ***(29).***

Many elements need to be considered in identifying IDUs with IE who may be appropriate for OPAT**(Table 3)**, the most highlighted are medications for opioid use disorder, safe housing, support for transportation, and need for multidisciplinary stakeholder ***(8).***

Table (3): Elements to consider in identifying IDUs with IE who may be appropriate for OPAT ***(8)***

Patient preference	• An open discussion of antibiotic options and venues for receiving antibiotics
Feasibility	• Does the patient have health insurance? Is home health accepting IDUs on OPAT? Is home health accepting home infusion company? • Availability of residential addiction treatment facilities or medical respite (for patients without stable housing) able to accept patients with peripherally inserted central catheter (PICC)? • Social work/case management consultation for exploring outpatient resources and support system.
Substance use disorder	• Patients with opioid use disorder engaged in treatment with medications for opioid use disorder, and when ongoing post-discharge care, including medications, is available, may be good candidates for OPAT. • Harm reduction education may be offered, including an open discussion of whether the PICC affects cravings or any desire to use drugs through the PICC.
Informed consent	• Must be able to provide informed consent and express understanding of risks of using the PICC for anything other than antibiotics. • Must be able to demonstrate understanding of how to self-administer antibiotics after teaching.
Home environment	• Presence of safe housing. • It is optimal if there are sober supports in the home willing to assist with home antibiotics and receive teaching from OPAT team or home infusion company. • A discussion of the home environment may include verification of running water, electricity, and a working telephone number.
Transportation	• Discuss whether the patient is able to obtain transport to and from clinic visits, including substance use disorder care. • Discuss willingness to attend frequent clinic visits.

- ***Management scheme in patients who can't complete 6 weeks of intravenous treatment***

For all patients who cannot complete 6 weeks of intravenous treatment (patients who are in stable condition, have no indications for cardiac surgery or extracardiac complications, and do not agree to stay in the hospital or to go to a skilled nursing facility), best practice would be to offer oral antibiotics to complete 6 weeks of treatment. Patient-centered decision-making is reasonable and includes a discussion of alternative antibiotic strategies ***(30)***.

There is clear evidence that step-down from intravenous to oral antibiotic therapy is superior to incomplete intravenous antibiotic treatment with lower all-cause readmission rates***(31)***.

A suggested approach for the timing of transitioning from intravenous to oral antimicrobial treatment is classified into 2 scenarios: planned and unplanned **(Figure 1)** ***(8)***.

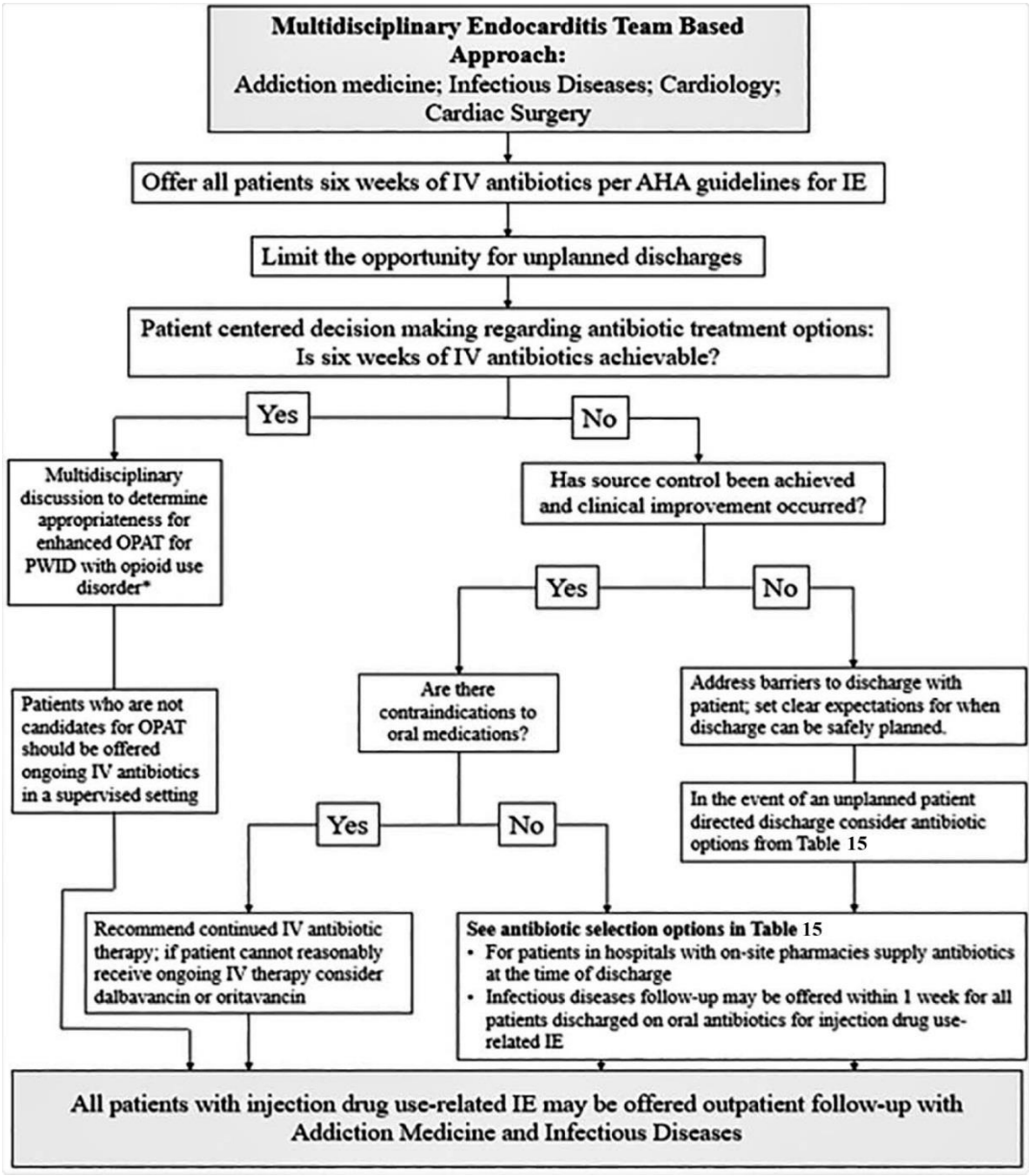

Figure (1): Approach for outpatient antimicrobial treatment in IDUs with IE***(8)***

Planned discharges occur after the patient with IE and the endocarditis team have discussed different treatment options for post-hospitalization care. In these scenarios, the optimal timing of switch from intravenous to oral therapy is currently undefined. However, planned step-down therapy to oral therapy may not be considered until clinical improvement has been documented, including blood culture clearance, surgical debridement of metastatic foci, and resolution of systemic manifestations (fever, chills, malaise). When possible, early discussion of alternative antibiotic strategies with a planned switch date to be established so that follow-up appointments can be scheduled before discharge and when available ***(8)***.

In case of unplanned patient directed discharge, consider antibiotic options from **(Table 4)**. Follow-up with infectious diseases specialists within 1 week of discharge would be reasonable for all patients discharged on oral or long-acting antibiotics, and referrals to addiction treatment and cardiology should be arranged ***(32)***.

- ***Antimicrobial management in patients with S. aureus IE who cannot complete 6 weeks of intravenous medication***

Currently, no evidence supports the superiority of any oral regimen, and regimen choice may be based on patient-specific data, including drug-drug interactions, gastrointestinal absorption, antimicrobial susceptibility results, and patient affordability.

Recently, the Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis (POET) trial -in which all patients initially received at least 10 days of intravenous antibiotics- showed that changing to oral antibiotic treatment was non-inferior to continued intravenous antibiotic treatment in patients with endocarditis who were in stable condition ***(29)***.

Some experts in IE have used a variety of oral treatment regimens with special considerations in IDUs with IE, which are listed in **(Table 4)**. These experts suppose that if an oral regimen is selected, then combination therapy with two active agents (based on susceptibility data) from different drug classes is preferred. According to some other experts, a single antibiotic was thought to be sufficient***(8).***

Table (4):Oral antibiotic therapy for IDUs with IE caused by S. aureus who can't complete I.V antibiotic regimens for 6 weeks ***(8)***

Regimen	Dose and route	Duration (weeks)
Methicillin-susceptible:		
Dicloxacillin	1 gm every 6 hours	≥ 6
Plus		
Rifampin	600 mg every 12 hours	≥ 6
Ciprofloxacin	750 mg every 12 hours	≥ 6
Plus		
Rifampin	300 mg every 8 hours	≥ 6
Methicillin - resistant:		
Linezolid	600 mg every 12 hours	≥ 6
Plus		
Rifampin	600 mg every 12 hours	≥ 6

❖ Surgical management of IDU-IE

According to the Society of Thoracic Surgeons Adult Cardiac Surgery database, in 2017, the prevalence of IDU-IE undergoing valve surgery was 41.1% ***(33).***

The 2016 American Association for Thoracic Surgery guidelines on the surgical management of IE emphasize that patients with IDU-IE have a greater probability of death in the year after operation than patients with non–injection drug use–related IE, and that patient management must include treatment for substance use disorder. In the absence of treatment for substance use disorder, IDUs have a higher risk of recurrent IE attributable to risk of recurrent injection drug use. Although there is no evidence that indications for valve surgery are different for IDU- IE than for patients who do not inject drugs and have IE, the application of these indications in IDUs has been heterogeneous. Some centers have opted for a more conservative approach to surgical intervention in IDUs, particularly in those with ongoing injection drug use and prior cardiac valve surgery ***(34).***

One other factor in cardiac valve surgical management of IDU-IE deserves comment is that IDU-IE often have complex cardiac involvement requiring long stays in the intensive care unit and hospital postoperatively, which can pose a heavy burden on hospitals. These factors may contribute in part to the development of risk-averse behavior and reluctance among surgeons to operate on this enlarging cohort ***(8).***

For the initial episode of cardiac valve surgery, early survival rates have been overall high, largely as a result of factors such as younger age and a lower rate of comorbid conditions that characterize the IDUs cohort. Recurrent IE and death after valve surgery have been prevalent in this population, however, especially in the setting of untreated substance use disorder***(35).***

- ***Indications for surgery in IDU-IE***

Given the high recurrence rate of IE due to continued drug abuse, surgery should generally be avoided in IDUs with right-sided native IE, but it should be considered in the following situations (all are class IIa recommendations):

- Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy.
- IE caused by organisms that are difficult to eradicate (e.g., persistent fungi) or bacteremia for at least 7 days (e.g., S. aureus, Pseudomonas aeruginosa) despite adequate antimicrobial therapy.
- Tricuspid valve vegetations> 20 mm that persist after recurrent pulmonary emboli with or without concomitant right HF***(22)***.

- ***Timing of surgery***

Only 5–16% of IDUs needs surgery. Although, left-sided IE has clear indications for early surgery, early surgery in right-sided IE is not established presently ***(36)***.

The strategy to delay surgery until the microbial therapy is accomplished and may decrease morbidity and mortality rates significantly. Early surgery is a choice in case of IE with Staphylococcus aureus or fungal infection. Early surgery of tricuspid valve IE is considered when associates atrial septal defect, prosthetic valve endocarditis, infected pacing leads, indwelling catheters and simultaneous left-sided IE. Additionally, development of bacteremia or pulmonary septic emboli also has early surgery ***(37)***.

- ***Types of valve surgery needed in IDU-IE***

The principles of surgery for tricuspid valve IE comprise debridement of infected tissue, excision of vegetations with valve conservation or valve repair and removal of the TV with its replacement. In case of native pulmonary valve, its preservation is usually recommended. If pulmonary replacement is mandatory, the utilization of a homograft or xenograft is favored ***(38)***.

Importantly, first line of surgical techniques in IDUs is vegetectomy and valve repair. Various techniques that are used in cardiac surgery for right-sided IE:

- Vegetectomy (excision of vegetations).
- Valvulectomy (total removal of valve leaflets and chordate tendineae).
- Valvectomy (valve excision).
- Reconstruction of the cusps (e.g., bicuspidization or conversion to a bicuspid valve).
- Pericardial patch augmentation.
- Kay's or De Vega's annuloplasty.
- Annuloplasty ring implantation.
- Synthetic or expanded polytetrafluoroethylene (PTFE) neo-chords.
- Valve replacement (bioprosthetic, mechanical prostheses) ***(37)***.

Valve repair is mainly achieved with autologous pericardial patch, artificial chordae, and simple annuloplasty with sutures (Kay's or De Vega annuloplasty). Ruptured chordae may be restored with PTFE neo-chordae. In a single perforated valve leaflet (cusp) can be used either untreated or glutaraldehyde-treated autologous or bovine pericardial patch. Pericardial patch reconstruction aims to avoid the use of any prosthetic materials. Autologous pericardial patch repairs small defects by direct closure in case of one leaflet. It is also used in wide excision or debridement of one leaflet or two leaflets ***(39)***.

Bicuspidalizationannuloplasty is done after total excision of the posterior leaflet of tricuspid valve. Importantly, septal leaflet excision of TV has high risk of postoperative atrio-ventricular block. This technique is accomplished either by Kay's annuloplasty or De Vega annuloplasty. Both Kay's annuloplasty and De Vega annuloplasty are the first choices indication for valve repair mainly in IDUs. After broad resection (>75%) of the anterior leaflet of TV, it is recommended using of prosthetic or pericardial annular ring ***(39)***.

Kay's annuloplasty is mainly done after the total resection of a leaflet, and it is accomplished by the placement of fixing sutures in the corresponding segment of annulus to create a bicuspid valve***(39)***.

De Vega annuloplasty(Figure 2) is based on fixing of two semi-circular purse string sutures between the anteroseptal commissure to the postero-septal commissure with tricuspid annular reduction. This leads to the coaptation of the residual two leaflets***(40)***.

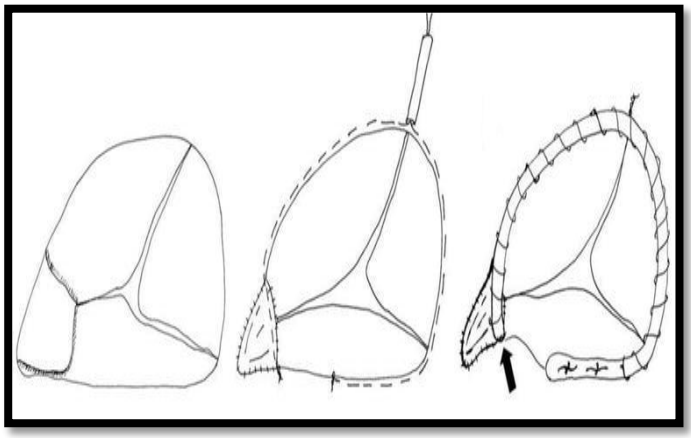

Figure (2):De Vagaannuloplasty of the tricuspid valve***(40)***

Valve replacement is required in case of a large destroyed valve with increased pulmonary pressures and pulmonary vascular resistance. It also requires the absence of drug addiction during surgery and after surgery.Presently, it is recommended tricuspid valve excision for right-sided IE in IDUs.Valve replacement in IDUs is correlated with greater risk for recurrent infection and redo surgery (re-operation). It seems that mechanical prostheses and xenografts have similar outcomes. However, recurrence of IE is mainly unchanged for mechanical and bioprosthetic valves. Placement of a bioprosthetic valve may be challenging in case of IDUs with endocarditis considering the low compliance of IDUs for any treatment, risk of recurrent infections, risk of redo surgery, or valve generation. HIV is not acontraindication for surgery having good prognosis after it.An important concern of tricuspid valve surgery is the damage of conduction system, which is higher in TV replacement when compared with TV repair***(41)***.

Taking into account the current guidelines of The European Association for Cardio-Thoracic Surgery, the first line recommendation (Class I) in IE for IDUs is the excision of infected tissue (vegetation) with valve repair. Furthermore, the second line recommendation (Class IIa) is tricuspid valve replacement. Bioprosthesis is the principal choice in TV replacement in IDUs, because mechanical valve needs long life anticoagulation***(39)***.

A conservative approach is recommended by European Society of Cardiology in case of IDUs which present greater risk of recurrent infection. When valve replacement is necessary, bioprosthesisdecreases the thromboembolism risk with no anticoagulant therapy on long term. On the other side, younger IDUs are disposed to redo surgery or re-operation either because of recurrent infection or valve degeneration **(Figure 3)**. Moreover, valvectomy is the last choice to valve repair or valve replacement in IDUs with greater risk of recurrent infection. The valvectomy technique eludes the use of prosthetic material but is limited by residual severe tricuspid regurgitation with right heart failure***(42)***.

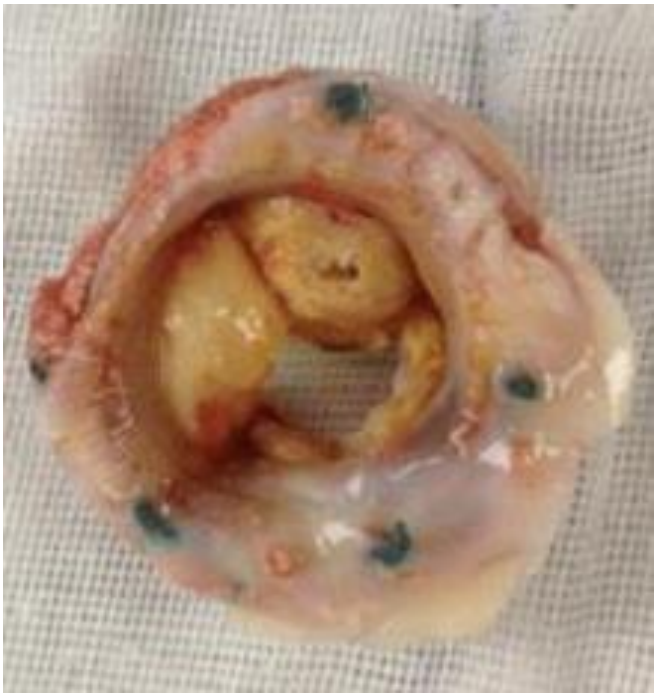

Figure (3):A damaged bioprosthetic tricuspid valve with vegetations***(42)***

- ***Catheter-based interventions in treatment of IDU-IE of the tricuspid valve***

To prevent further septic pulmonary embolism, percutaneous debulking of vegetations may be an alternative to open surgery in right-sided IE. Aspiration vegectomy with veno-venous bypass and filtrations with the AngioVac system (AngioDynamics) or other systems is an option that has been adopted most often in patients deemed to be at high surgical risk. It has also been used in lower-risk patients with vegetations and no significant tricuspid regurgitation for whom debulking is deemed appropriate ***(43).***

Aspiration can remove vegetations and thrombus associated with right-sided valves and cardiovascular implantable electronic device leads,

but it does not treat valve dysfunction and may unmask or potentially contribute to exacerbation of tricuspid regurgitation. Valve repair is expected in patients with significant regurgitation who meet surgical criteria, although it may be a temporizing option to facilitate medical management toward stabilization and ultimate surgical intervention ***(8).***

❖ Prognosis of IDU-IE

Recurrence of IE is characteristically for IDUs. Higher mortality in IDUs with right-sided IE is associated with vegetations>20 mm, S. aureus and fungal endocarditis, polymicrobial IE, concomitant left-sided IE and late presentation in critical condition. To sum up, the early and complete surgical debridement of infected tissue together with microbial therapy assures a good prognosis on long term***(44)***.

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