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Infective Endocarditis in Intravenous Drug Users: Surgical Treatment

Moldovan Horatiu, Adrian Molnar, Victor Costache
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Abstract

Intravenous drug use is associated with infective endocarditis. Besides, it does appear that left-sided infective endocarditis is a feature of general population, whereas right-sided infective endocarditis is common in intravenous drug users. The most common etiology of right-sided infective endocarditis in intravenous drug users is *Staphylococcus aureus* in about 75% followed by streptococci, Gram-negative bacilli and fungi. In case of intravenous drug users with infective endocarditis, optimal treatment strategies lack a general consensus. Additionally, the best indication and timing of surgery are debatable. To overcome these problems, the early and complete surgical debridement of infected tissue together with microbial therapy assures a good prognosis in the long term.

Keywords: endocarditis, drug-associated endocarditis, intravenous drug abuser endocarditis, intravenous drug users, right heart endocarditis

1. Introduction

Infective endocarditis (IE) is a rare infectious disease with elevated morbidity and mortality [1]. Intravenous drug use is associated with infective endocarditis (IE) [2]. To the best of our knowledge, IE accounts for 2–5% per year among the intravenous drug users (IDUs) [3–6]. Approximately 41% of IDUs with bacteremia will develop IE [7]. Conversely, it is widely agreed that intravenous drug users (IDUs) diagnosed with IE are mainly white young males [8–12].

Right-sided infective endocarditis has been mainly defined among IDUs [13–15]. Generally, right-sided IE comprises 5–10% of cases with IE [16–18]. It does appear that left-sided IE is a feature of general population, whereas right-sided IE is common in IDUs [19–21]. To further characterize, IDUs may present in 86% cases right-sided IE, whereas 14% have left-sided IE with or without right-sided IE [21]. However, some older data outlines that the IDUs group may present equal incidence of left-sided and right-sided IE [22].

Common *predisposing factors* for right-sided IE are the intravenous drug users (IDUs), catheter-related infections, pacemaker or defibrillators wires, intracardiac devices (catheters for hemodialysis; tricuspid prosthetic valve), right heart catheterization, congenital heart defects, sepsis, and alcoholism [13–15, 23]. In case of

the right-sided IE, tricuspid valve is affected in 90% cases [21], whereas pulmonic valve represents about 10% from right-sided IE cases [3, 18, 24]. Up to now, isolated right-sided IE involving the pulmonary valve, the eustachian valve, interventricular septum, or right ventricular free wall have been described [17, 21, 25].

2. Microbiology

According to current evidence, IE among IDUs presents a large spectrum of microbial pathogens (**Table 1**) [26–31].

Pathogens as *Pseudomonas aeruginosa*, other gram-negative microorganisms, fungi, enterococci, streptococci, and polymicrobial infections occur less frequently [16]. Importantly, other pathogens noted in IDUs are oral bacteria such as *Prevotella intermedia*, *Haemophilus parainfluenzae*, *S. constellatus*, and *E. corrodens* [32–36].

The most common etiology of right-sided IE in IDUs is *Staphylococcus aureus* (*S. aureus*) in about 75% [1, 4, 6, 37–39] followed by streptococci, Gram-negative bacilli, and fungi [40]. In fact, published data supports the involvement of *S. aureus* among IDUs in 40–74% cases of IE [38, 41, 42]. *S. aureus* is the most common cause of tricuspid valve endocarditis regardless of associated risk factors in IDUs [1, 4, 16, 18, 43].

The incidence of negative blood cultures is reported as 2.5–31% and is associated with delayed diagnosis and treatment [44], with large vegetations [45], and with highest morbidity and mortality [16, 45, 46].

Regarding HIV, a prevalence of HIV as high as 60% among IDUs has been reported by centers from Europe and the USA [11, 40]. HIV is more common among IDUs with right-sided IE than left-sided IE [47].

Polymicrobial endocarditis is characteristically for IDUs [48] and may involve microorganisms such as *Bartonella* spp., *Candida* spp., or *Tropheryma whipplei* [49]. 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* [50–52].

-
- *Staphylococcus aureus* and coagulase-negative staphylococci,
 - group A streptococci,
 - *P. aeruginosa*,
 - HACEK organisms (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*),
 - Tetanus (*Clostridium tetani*),
 - Anthrax (*Bacillus anthracis*),
 - wound botulism (*Clostridium botulinum*),
 - tuberculosis,
 - diphtheria (*Corynebacterium diphtheriae*),
 - viruses (HIV, HBV with HDV, HCV, and HTLV),
 - fungal infections (*Candida* spp. and *Aspergillus* spp.),
 - parasitic infections (malaria and leishmaniasis)
-

Table 1.

Spectrum of microbial pathogens may constitute comorbidity in IDUs [26–31].

3. Diagnosis

History and classic Oslerian manifestations (persistent bacteremia or fungemia, active valvulitis, immunological vascular phenomena, and peripheral emboli) help with a straightforward diagnosis in IE [1]. Typical clinical manifestations of IE comprise fever, positive blood cultures, and valvular vegetations on echocardiography [53]. IE should be suspected in the presence of fever and embolic phenomena [16]. Persistent fever and bacteremia are common manifestations of tricuspid valve IE [16].

Clinical manifestations are usually limited in the early IE of IDUs, right-sided endocarditis and *S. aureus* [1]. Right-sided IE mainly present fever, cough, hemoptysis, dyspnea caused by pulmonary emboli, anemia, and no systemic emboli [23]. Characteristically, right-sided IE does not develop immunological vascular phenomena (splinter hemorrhages, Roth spots, and glomerulonephritis) and the peripheral emboli [1]. Right-sided IE can be associated with septic pulmonary emboli [1]. In fact, pulmonary embolism is often present in right-sided IE and pacemaker wires IE [16].

Usually, the association of clinical findings, positive blood cultures, and positive echocardiography set up the diagnosis [23]. However, these typical clinical manifestations of IE are often absent among IDUs, especially in those infected with *S. aureus* and HACEK (*Haemophilus species*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*) [54]. Common complications of right-sided IE are valvular regurgitations, cardiac abscess, and septic pulmonary emboli [55].

Relapse and reinfection are two types of recurrence [16]. Basically, recurrence within 6 months of same IE produced by same microorganisms is termed *relapse* [55]. Reinfection or recurrent IE refers to the *recurrence* of same IE with same microorganisms after 6 months from initial episode [53]. Recurrent IE has higher frequency in IDUs with increased valve replacement [16] with a reported incidence as 41% [56].

The landmark lesion of IE is the *vegetation* (**Figure 1**) [57]. In this context, IDUs population with vegetations >20 mm may present higher embolic risk [58] and higher mortality as well [25, 58, 59].

The cornerstone of imaging diagnosing for infective endocarditis is echocardiography [16]. Transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TOE) are vital in the diagnosis of any IE [16]. TTE is the first line recommendation either for native valve endocarditis or for prosthetic valve endocarditis. In case of suspected native valve endocarditis, TTE has a sensitivity of 50–90% and a specificity of 90% [60]. For IE with vegetation, TTE has a moderate sensitivity (75%) and high specificity (>90%) [61]. For suspected prosthetic valve endocarditis, TTE has a reduced sensitivity of 40–70%. However, TTE comes up with significant information regarding ventricular size and function, and “hemodynamic severity of valve lesions” [60]. Major criteria in the diagnosis of IE are represented by three echocardiographic features: vegetation, abscess or pseudoaneurysm, and prosthetic valve with new dehiscence [16]. Moreover, TTE provides useful information in the diagnosis of anterior prosthetic aortic valve abscesses, which are difficult to be seen on TEE [60].

TOE is recommended when TTE is nondiagnostic or positive, suspected complications, or in presence of intracardiac device leads [60]. In case of native valve endocarditis, TOE has a sensitivity of 90–100% and a specificity of 90% for revealing vegetations. As such, TOE is highly superior to TEE regarding the detection

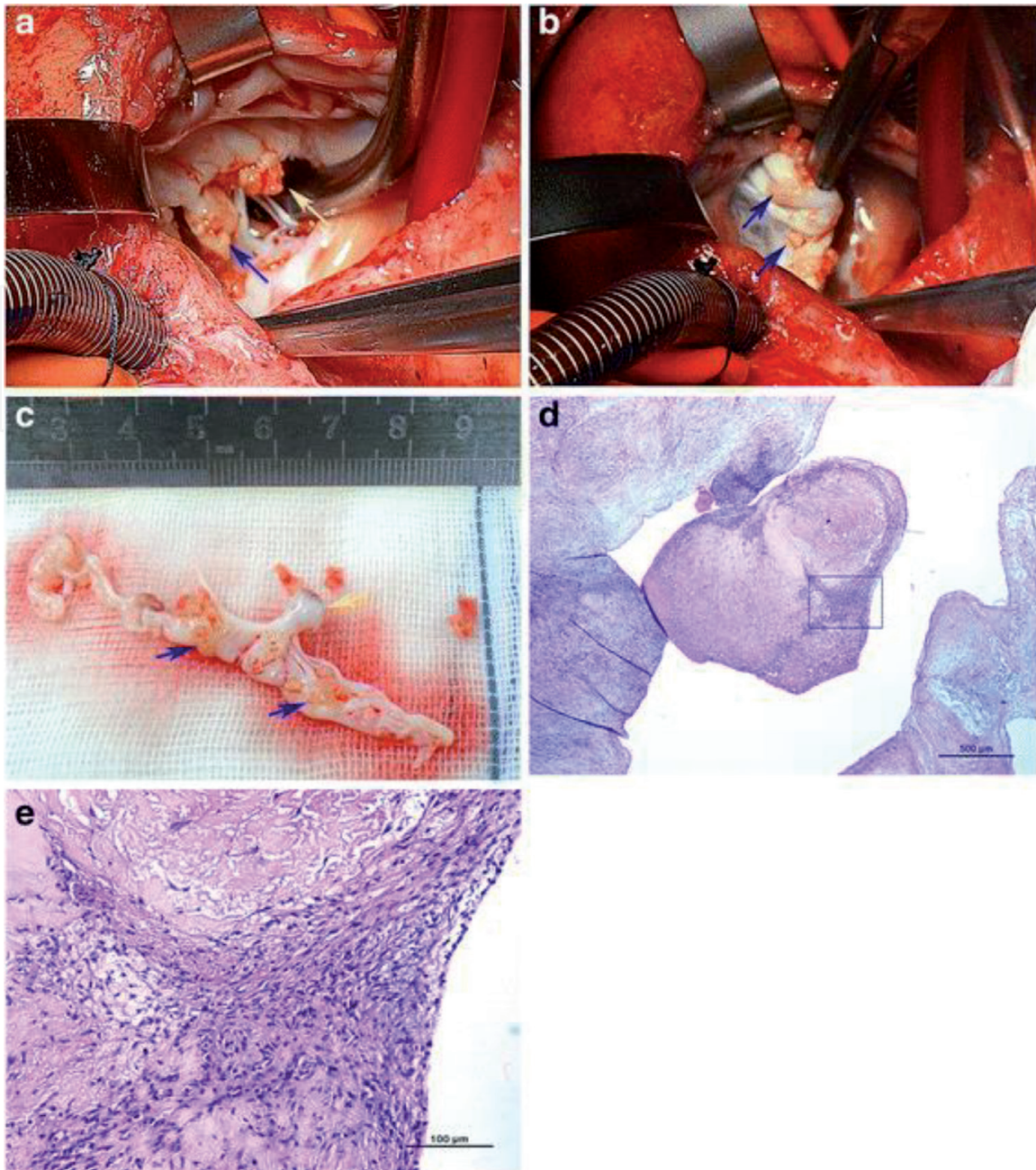


Figure 1.

Macroscopy and microscopy of the involved tricuspid valve and vegetation. (a) Yellow arrowhead: the large vegetation, blue arrowhead: rupture main chordae tendineae. (b) Blue arrowheads: multiple verrucous nodular vegetation on the atrial surface of leaflet. (c) Resected tricuspid valve. Blue arrowheads: multiple small vegetations, yellow arrowhead: rupture main chordae tendineae. (d) Microscopy of the vegetation adhered to the leaflet, magnification 4×, hematoxylin and Eosin stain. (e) Enlarged square area in (e) showing inflammatory cell infiltration and fibrin-platelet thrombi, magnification 20×, hematoxylin and Eosin stain. NOTE: every figure specifies this sentence beginning: From Bai et al. [57]. It is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

of abscesses, perforations, and fistulae [60]. TOE has higher sensibility in the detection of pulmonary vegetations [62]. When clinical manifestations sustain IE with negative or unclear TTE, TOE has high sensitivity (>90%) and may reveal: (1) vegetations; (2) paravalvular or intracardiac abscess, (3) new valvular regurgitations, and (4) prosthetic valve dehiscence (**Figure 2**) [57, 63, 64].

Currently, 3D TOE provides useful information about the morphology and size of vegetation, evaluation of perivalvular extension, dehiscence of prosthetic valve, and valve perforation [65].

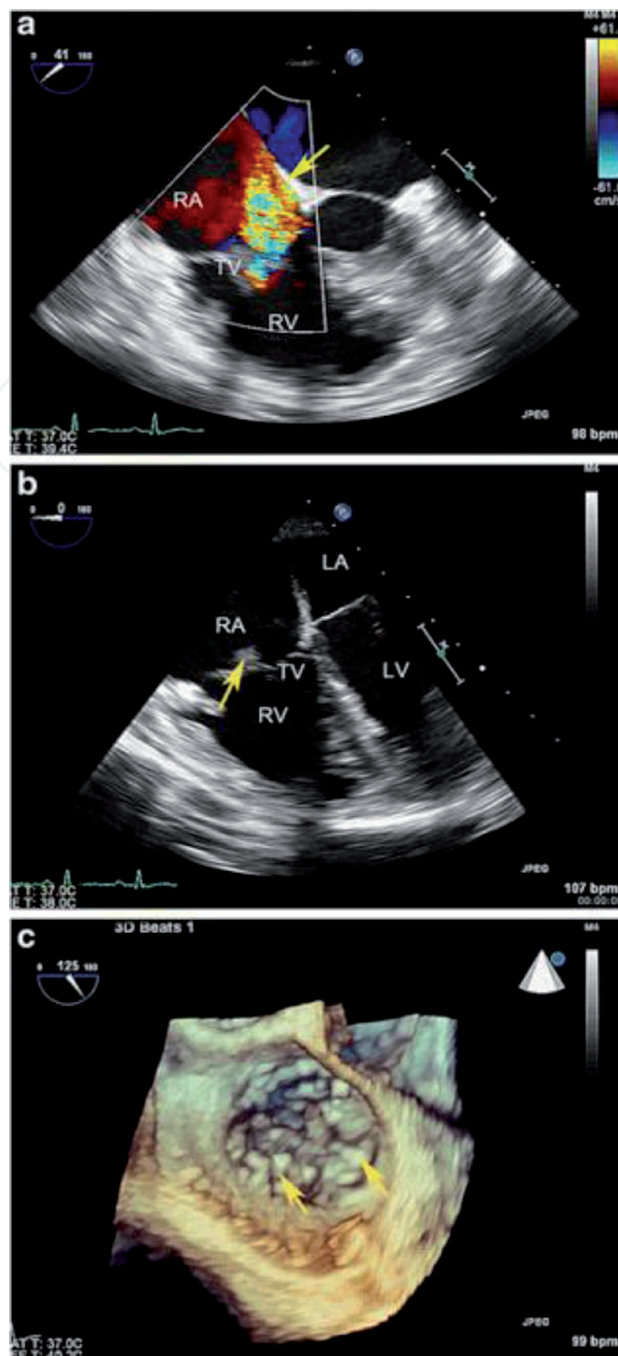


Figure 2. Transesophageal echocardiography images of the patient before surgery. (a) Tricuspid regurgitation, Yellow arrowhead: wide and reversed blood flow signals at TV site. (b) A large vegetation formation. Yellow arrowhead: a large vegetation adheres to anterior leaflet of TV. (c) Suspicious multiple vegetations on 3D echo image. Yellow arrowheads: multiple verrucous abnormal nodular projections on the leaflet surface. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle, TV tricuspid valve. NOTE: every figure specifies this sentence beginning: From Bai et al. [57]. It is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Other imaging techniques such as magnetic resonance imaging (MRI), multislice computed tomography (MSCT), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) are also valuable for the diagnosis of IE [16]. MSCT, MRI, and cardiac CT can provide greater information when compared with TEE regarding either paravalvular anatomy or complications (e.g. mycotic aneurysms, paravalvular abscesses) with lesser prosthetic valve artifacts [60]. Currently, using CT imaging in the diagnosis of paravalvular lesions is a major criterion in the 2015 ESC guidelines on IE [16].

Modified Duke criteria (2000) for diagnostic classification are well-known [64] and reviewed by 2015 ESC Guidelines for the management of infective endocarditis [16]. Only that, these modified Duke criteria have poorer diagnostic precision in the early diagnosis of IE from IDUs, which present fewer typical clinical manifestations [16]. The addition of imagistic techniques cardiac/whole-body CT scan, cerebral MRI, ^{18}F -FDG PET/CT, and radiolabelled leucocyte SPECT/CT may increase accuracy of the modified Duke criteria in IDUs. To sum up, these modified Duke criteria are useful, but they do not substitute the decision of a multidisciplinary team or of the “Endocarditis Team” that is defined later [16].

4. Treatment

The initial treatment of IE is empirical in majority of cases [1]. Consistent with published data, the main effective treatment is medical therapy, whilst surgery is a choice in smaller cases [16]. So that, medical treatment in right-sided IE of IDUs is usually effective with good prognosis up to 80% cases [16, 23, 66].

S. aureus is the most frequent cause of IE in IDUs; as a result, medical treatment should cover this pathogen [16]. Short courses of antimicrobial therapy in right-sided IE with *S. aureus* in IDUs assure high cure rates (>85%) [1].

A short course (2 weeks) with oxacillin or cloxacillin is mainly sufficient [16]. Initial therapy comprises penicillinase-resistant penicillins, vancomycin, or daptomycin in combination with gentamicin [16]. Short course (2 weeks) with oxacillin or cloxacillin is mainly efficient for isolated tricuspid IE with good compliance to therapy, vegetation <20 mm, MSSA, without empyema or other metastatic sites of infection, without prosthetic valve or left-sided IE, without cardiac/extracardiac complications and without severe immunosuppression (<200CD4 cells/ μL) with/without AIDS. Anti-pseudomonas agent should be added in pentazocine addict [59]. Antifungal therapy for *Candida* spp. is added when an IDU utilizes brown heroin combined with lemon juice [67].

A traditional approach for the treatment of right-sided IE is the regimen formed from gentamicin with nafcillin or oxacillin. Another approach of IDUs with right-sided *S. aureus* IE and no other complications (e.g. aortic or mitral valve involvement, extra pulmonary infections or meningitis, renal failure, MRSA infection) is the antimicrobial coverage with short-course (2 weeks) of beta-lactam plus aminoglycoside that may be greatly successful [1]. Current guidelines still suggest the use of gentamicin, but some available data suggest that it might be unnecessary [68].

Moreover, daptomycin monotherapy is approved for the therapy of *S. aureus* bacteremia or right-sided *S. aureus* IE [69]. If laboratory evaluation shows opiate withdrawal, 10–20 mg of long-acting methadone can be prescribed until the regular doses are established [70].

To sum up, it is problematic to treat IE in IDUs because of the frequent exposures to virulent microorganisms; poor compliance with treatment; illegal drug use or withdrawal manifestations during hospitalization; opioid maintenance therapy; and early self-discharge or long hospitalization [70, 71]. Regardless of correct antimicrobial therapy, IDUs develop *relapsing IE* [56, 72, 73].

5. Surgery

Surgery is not a contraindication for IDUs with IE [4]. However, surgery indications are complex and are based on the clinical manifestations, associated risk factors (e.g. age, microorganisms, size of vegetation, perivalvular infection, embolism,

heart failure, and other associated comorbidities) and the expertise of surgery team [1]. A multidisciplinary team or the “Endocarditis team” with knowledge in cardiology, infectious diseases, microbiologists, imaging, neurologists, neurosurgeons, and cardiothoracic surgery should provide decisions regarding the indication and timing of surgery [1]. Cardiac surgery in IDUs with IE aims to remove infection with hemodynamics stabilization hemodynamic may be suggested for IDUs [74].

In terms of surgery, right-sided IE has better outcomes than left-sided IE [1]. General approach of IDUs with right-sided IE is medical therapy and to delay as much as possible the use of valve prostheses [1].

Surgical treatment indications for right-sided IE are following [1, 16, 28, 75]:

- TV vegetations >20 mm after recurrent septic pulmonary emboli with or without right heart failure;
- Severe tricuspid regurgitation with right heart failure unresponsive to medical therapy;
- IE with fungi or persistent bacteremia with virulent microorganisms for at least 7 days (e.g., *S. aureus*, *P. aeruginosa*) regardless of the antimicrobial therapy.

5.1 Timing of surgery

Only 5–16% of IDUs needs surgery [76–78]. However, if left-sided IE has clear indications for early surgery, and the indications for early surgery in right-sided IE are not established presently [79].

The strategy to delay surgery until the microbial therapy is accomplished and may decrease morbidity and mortality rates significantly. In keeping with published data, *early surgery* is a choice in case of IE with *Staphylococcus aureus* or fungal infection [1, 16, 80]. Early surgery of tricuspid valve IE is considered when associates (1) atrial septal defect; (2) prosthetic valve endocarditis; (3) infected pacing leads; (4) indwelling catheters; and (5) simultaneous left-sided IE [81, 82]. Additionally, development of bacteremia or pulmonary septic emboli also has early surgery.

5.2 Surgical techniques

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 [16, 76, 81]. 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.

Various techniques that are used in cardiac surgery for right-sided IE [71, 81, 82]:

- vegetectomy (excision of vegetations)
- valvectomy (total removal of valve leaflets and chordate tendineae)
- valvotomy (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).

Importantly, first line of surgical techniques in IDUs is vegetectomy and valve repair [23].

Valve repair is mainly achieved with autologous pericardial patch, artificial chordae, and simple annuloplasty with sutures (Kay's or De Vega annuloplasty) [23]. Ruptured chordae may be restored with polytetrafluoroethylene neo-chordae [16].

In a single perforated valve leaflet (cusp) can be used either untreated or glutaraldehyde-treated autologous or bovine pericardial patch [16]. **Pericardial patch reconstruction** aims to avoid the use of any prosthetic materials [23]. 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 [23].

Bicuspidalization annuloplasty 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 [23]. 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 [23]. After broad resection (>75%) of the anterior leaflet of TV, it is recommended using of prosthetic or pericardial annular ring [23].

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 [23].

De Vega annuloplasty (Figures 3 and 4) is based on fixing of two semi-circular purse string sutures between the anteroseptal commissure to the posteroseptal commissure with tricuspid annular reduction [23, 83]. This leads to the coaptation of the residual two leaflets.

Valve replacement. Valve replacement is *required* in case of a large destroyed valve with increased pulmonary pressures and pulmonary vascular resistance [16, 76, 81]. It also requires the absence of drug addiction during surgery and after surgery [23]. Presently, it is recommended tricuspid valve excision for right-sided IE in IDUs [23].

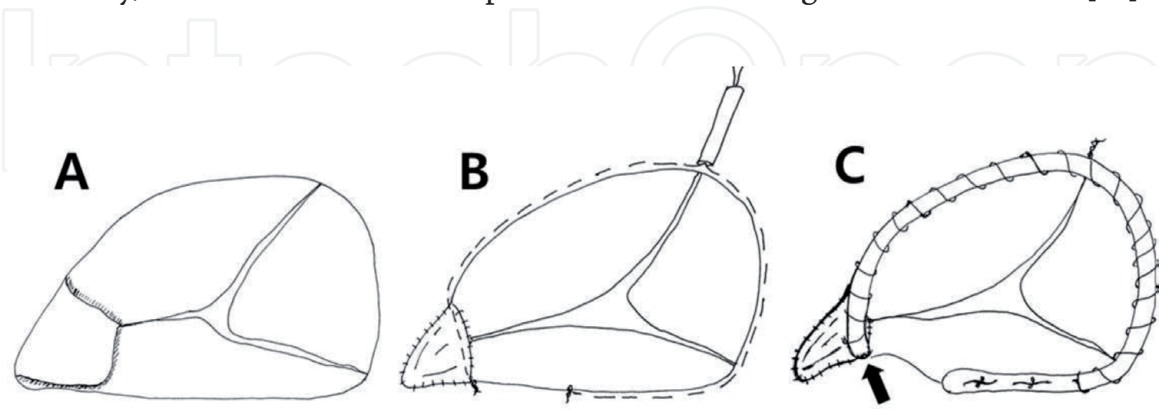


Figure 3.

Operative procedures. (A) After the prolapsed leaflet segments and chordae were excised, the anterior commissural defect was made. (B) The defect was closed with an elliptical pericardial patch of 2.0 × 1.0 cm size. An adjustable DeVega-type annuloplasty using two continuous 5-0 Polypropylene sutures was performed to select an appropriate-size ring for complete leaflet coaptation. (C) A 26-mm Edward MC₃ ring was placed using two interrupted, pledgeted 2-0 Dacron sutures and two continuous 3-0 polypropylene sutures. The anterior horn of the rigid ring (black arrow) was sutured to the medial end of the patch. NOTE: every figure specifies this sentence beginning: From Kim et al. [83]. It is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

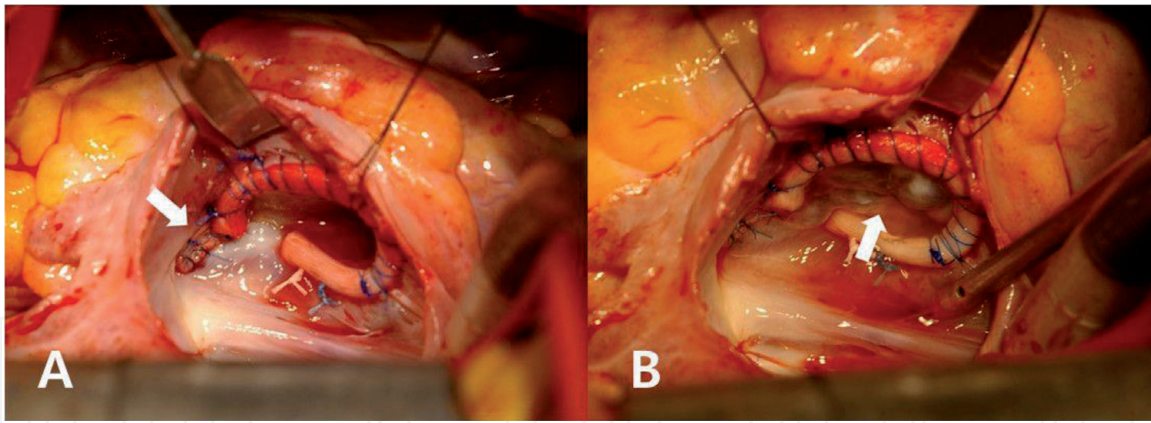


Figure 4. Operative findings. (A) The anterior commissure defect was closed with a patch (white arrow) and a rigid ring was placed along the functional valve opening. (B) The valve leaflets showed complete coaptation (white arrow) on saline test. NOTE: every figure specifies this sentence beginning: From Kim et al. [83]. It is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Valve replacement in IDUs is correlated with greater risk for recurrent infection and redo surgery (re-operation) [81]. It seems that mechanical prostheses and xenografts have similar outcomes [16]. However, recurrence of IE is mainly unchanged for mechanical and bioprosthetic valves [84]. 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 a contraindication for surgery having good prognosis after it [85].

An important concern of tricuspid valve surgery is the damage of conduction system, which is higher in TV replacement [81, 86]. For instance, in case of 910 surgeries for tricuspid valve IE, there was higher risk of heart block in TV replacement (16%) versus TV repair (3%, $p < 0.0001$) [86].

Despite of published data supporting the greater risk of morbidity and mortality for multiple valve endocarditis [87], Weymann et al. outlined that single-valve endocarditis or multiple valve involvement have no different operative or postoperative risks [88]. In any type of prosthesis, survival on long-term is similar in any tricuspid valve replacement with prosthesis [89, 90]. Homograft tissue valve may be used after valvectomy mainly with cryopreserved mitral homograft [23].

IDUs have a greater mortality rate in comparison with the general population [91, 92]. However, right-sided IE treated surgically has good outcomes in the early, mid-term, and long-term [86]. Significant risk factors for poor prognosis in IDUs treated surgically are interrelated with the *Staphylococcus aureus* and fungi or polymicrobial IE, late presentation in critical condition, with the vegetation size, and with left-sided IE [93].

Taking into account the current guidelines of The Society of Thoracic Surgeons Workforce on Evidence Based Surgery, European Society of Cardiology, and The European Association for Cardio-Thoracic Surgery, the **first line recommendation** (Class Ia) 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 [16, 23, 39, 81, 94, 95].

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, bioprosthesis decreases the thromboembolism risk with no anticoagulant therapy on long term. On the other side, younger IDUs are disposed



Figure 5.

The damaged bioprosthetic tricuspid valve with vegetations. NOTE: every figure specifies this sentence beginning: From Chen et al. [96]. It is an open access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

to redo surgery or re-operation either because of recurrent infection or valve degeneration (**Figure 5**) [16, 96]. 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. Published data supports this technique because of its long-term survival after complete valvectomy. For instance, one study of Gaca et al. reports tricuspid valvectomy as first choice only in 66 cases from 910 patients (7.3%) [86].

Recurrence of IE is characteristically for IDUs [23, 97]. However, the best indication and timing of surgery are debatable [98]. Prognosis of IE in IDUs has good outcomes with mortality <5% [23]. Right-sided IE has a good prognosis with lower in-hospital mortality. As well, right-sided IE has a lower morbidity and mortality with better prognosis than left-sided IE but with greater early mortality rate [11, 21, 99]. Higher mortality in IDUs with right-sided IE is associated with vegetations >20 mm, fungal endocarditis, bacteremia, and older age [4, 13, 21, 59]. To sum up, the early and complete surgical debridement of infected tissue together with microbial therapy assures a good prognosis on long term [88].

6. Conclusions

Right-sided IE is the primarily disease that affects IDUs and patients with congenital heart diseases [16]. Diagnostic findings comprise fever and respiratory symptoms [16]. In the main part of cases, *S. aureus* is responsible pathogen [16]. For IDUs with IE, optimal treatment strategies lack a general consensus. Majority of

strategies are applied based on the team experience and the patient. Furthermore, this absence of evidence-based guidelines highlights that any IE should be managed by an “Endocarditis Team” [86]. Surgery is a choice only for difficult evolution, failure of medical therapy, or recurrent septic emboli to the lungs or paradoxical emboli [16].

Conflict of interest

There are no disclosures.

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