Infective endocarditis in intravenous drug users: a review article

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ABSTRACT

Approximately 10% of infective endocarditis (IE) involves the right side of the heart with the majority of these cases occurring in intravenous drug users. Patients are less likely to present with classical IE signs of a new murmur and peripheral stigmata, are more frequently immunocompromised and often have significant social difficulties. These factors result in both diagnostic and therapeutic challenges in this patient group that are not often seen in other patient populations with IE.

INTRODUCTION

This article aims to provide an overview of the current understanding of infective endocarditis (IE) in intravenous drug users (IVDUs) for a practising clinician. This includes the presentation, diagnosis and management of IE with reference to the difficult behavioural and social circumstances encountered in IVDUs, all of which interplay to form a challenging yet interesting clinical entity.

EPIDEMIOLOGY

Overall, the incidence of IE was stable between 1950 and 2000 at 3.6–7.0 cases per 100 000 patient years according to US population studies.[1] However, during that time the predisposing risk factors for the development of IE have changed significantly. This is as a result of the increasing use of intracardiac devices and haemodialysis, an ageing population with degenerative valve disease and intravenous drug misuse. Specifically, intravenous drug use was shown to be a predisposing risk factor in just under one-third (29.5%) of right-sided IE cases in a literature review of 262 patients from 2008 to 2013.[2] This represents the single largest risk factor identified in right-sided IE.

Among the IVDU population, IE is more frequently seen in males,[3] patients with HIV infection[4] and also affects younger patients when compared with IE in non-IVDU populations.[5]

AETIOLOGY

The most common micro-organism in all cases of IE in IVDU is *staphylococcus aureus* accounting for 68% of cases compared with 28% of IE in non-drug misusers.[6] Streptococci and enterococci are prone to infect abnormal aortic and mitral valves and make up the second and third most common pathogens, respectively, among IVDUs with IE.[1] Pseudomonal and fungal endocarditis, mostly *Candida albicans*, are also observed more frequently in IVDUs.[7] Polymicrobial endocarditis occurs primarily in IVDUs compared with non-drug misusers, generally due to staphylococcal, streptococcal and pseudomonal infection.[8] In addition, relatively non-pathogenic organisms such as *Haemophilus parainfluenzae, Eikenella corrodens* and *Streptococcus milleri*, which are normal oropharyngeal flora, can cause IE in IVDUs due to the use of saliva on injecting equipment.[8]

Concerning IE, there is a stark contrast between the valves involved in the IVDU and non-IVDU populations. As previously stated, only 13% of IE occurs on right-sided valves among all patient cohorts.[6] However, a Spanish study of 1529 IVDUs with IE, over a 15-year period, found that 79% of cases were right-sided (with 16% left-sided and 5% mixed).[9] The reason for this vast difference is yet to be clarified but may be partly explained by behaviours surrounding injection in IVDUs.

There are a number of factors resulting from intravenous drug use that predisposes to IE. First, illicit drugs are not pure and materials such as talcum powder and other particulate matter are often added to the drugs to increase their profitability. These contents can damage the endocardium and continued use may cause subclinical damage to the tricuspid valve.[10] This and the introduction of bacteria into the venous circulation at the time of injection may explain the increased incidence of right-sided endocarditis, in particular the tricuspid valve in the IVDU population.

Second, the active substance injected may play a role in the development of IE. Cocaine injection can cause tissue or skin damage, mediated via vasospasm, which in turn can increase the risk of developing IE.[11]

Finally, evidence shows that there may be a predilection for certain micro-organisms in IVDUs as a result of the preparation and injection of drugs. Due to poor hygiene and sterilisation at injection, IVDUs are prone to directly injecting micro-organisms present on the skin such as fungi or bacteria. In addition, it has been shown that IVDUs may have higher rates of skin colonisation with *S. aureus* than drug users only using oral drugs[12] or non-drug users.[13] Another small study analysed the relationship between staphylococcal endocarditis in IVDUs and skin colonisation with *S. aureus* by performing skin and blood cultures in a cohort of 20 IVDU patients with IE. The authors found that the same strain of *S. aureus* was implicated in IE as isolated on the skin cultures in all 12 patients with confirmed IE who were cultured within 72 h.[14] This may account for the high rates of *S. aureus* IE in IVDUs.

Figure 1 summarises the multiple factors involved in injection of drugs. This may explain why patients who inject drugs are known to represent one of the largest cohorts of patients at risk of right-sided IE.

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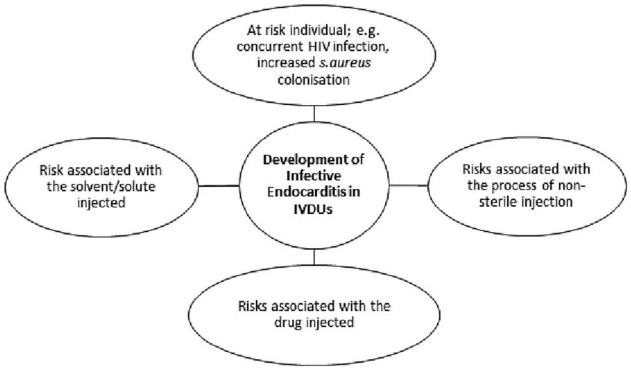

Figure 1 Factors influencing increased infective endocarditis (IE) incidence among intravenous drug users (IVDUs).

PRESENTATION

The signs and symptoms of IE are heavily dependent on the valve(s) involved and the responsible organism. In IVDUs, IE is normally right-sided with the tricuspid valve most commonly affected in 46%–78% of cases.[1 9] Often there are no specific clinical signs to suggest tricuspid valve endocarditis as murmurs are frequently inaudible and the classical peripheral stigmata of IE (Osler nodes, splinter haemorrhages, Roth spots) and heart failure are very rare.[1] However, general features such as pyrexia and cachexia are often present.

Despite evidence of septic pulmonary emboli in 80% of population studied with right-sided IE, the specific symptoms of septic pulmonary emboli were surprisingly uncommon; dyspnoea, chest pain and cough were only seen in 22%, 18% and 11%, respectively, of all right-sided endocarditis cases in a recent literature review.[2]

Most IE in IVDUs is staphylococcal and these patients are extremely susceptible to metastatic infection. Ruotsalainen *et al*[15] found that 85% of *S. aureus* endocarditis in IVDUs was complicated by extracardiac infection, most commonly pneumonia, abscess formation and osteomyelitis.

Non-specific, systemic symptoms such as fever, chills, anorexia, weight loss and malaise are common to IE affecting both sides of the heart (see table 1). This vague and non-specific presentation led an article from 1962 to label IE as 'the notorious deceiver',[16] which perfectly encapsulates its heterogeneous and ambiguous presentation. Consequently, heightened clinical suspicion is required from the outset to effectively investigate and ultimately diagnose IE. In particular, the diagnosis of IE should be actively considered in any IVDU presenting with pyrexia.

Table 1 Clinical features of infective endocarditis in all populations[1]

Symptoms (percentage of patients)	Signs (percentage of patients)
Fever (80–85), chills (42–75), sweats (25)	Pyrexia (80–96)
Anorexia (25–55)	New or changing murmur* (10–40)
Weight loss (25–35)	Neurological abnormalities* (30–40)
Malaise (25–40)	Embolic event (systemic* or pulmonary†) (20–40)
Dyspnoea (20–40)	Splenomegaly (15–50)
Cough (25)	Clubbing (10–20)
Stroke* (13–20)	Peripheral stigmata*
Headache (15–40)	▶ Osler nodes (7–10)
Nausea and vomiting (15–20)	▶ Splinter haemorrhages (5–15)
Chest pain† (8–35)	▶ Petechiae (10–40)
Myalgia and arthralgia (15–30)	▶ Janeway lesions (6–10)
	▶ Roth spots (4–10)

*More commonly seen in left-sided IE.†More commonly seen in right-sided IE.
IE, infective endocarditis.

DIAGNOSIS

Owing to the non-specific presentation of IE, the differential diagnosis is extensive, encompassing systemic (mostly autoimmune or rheumatological) and cardiac conditions (table 2).

Establishing a diagnosis of IE is not dependent on a single conclusive investigation or result, rather, it relies on multiple findings to be interpreted with the patient's clinical features. Given the varied presentation of IE the Duke criteria were proposed in 1994 and, in turn, Li *et al*[17] published the revised Duke criteria in 2000 to aid clinicians in the diagnosis of IE. The modified Duke criteria are widely regarded as the gold standard in diagnosis IE and are summarised in box 1.

Definitive diagnosis of IE can be ascertained on pathological grounds by meeting the following criteria:

- Micro-organisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolised or in an intracardiac abscess or
- Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis.

Alternatively, a definite diagnosis can be made clinically once both major criteria are met, one major and three minor criteria or five minor criteria are met (see box 1). The major criteria rely upon demonstrating positive echocardiogram findings of IE *and* proving existence of a micro-organism by culture or histologically.

Diagnosis of IE is *possible* if one major and one minor criteria, or only three minor criteria are met.

Thus, the two fundamental investigations for a clinician suspicious of IE are echocardiography and blood cultures.

INVESTIGATIONS

The role of echocardiography in identifying a vegetation, abscess or new regurgitation is critical (figure 2). The choice of transthoracic (TTE) versus transoesophageal echocardiography (TOE) needs careful consideration. TOE is shown to have a higher sensitivity of detecting vegetations in native valve endocarditis (NVE) and prosthetic valve endocarditis, but is more expensive, invasive and less immediately available.[1] Studies have also shown that TOE can be ineffective in changing the decision to treat in patients with a high probability of NVE based on TTE findings and clinical presentation.[1]

The American College of Cardiology and American Heart Association (ACC and AHA) recommend TTE in patients with

Table 2 Differential diagnosis of infective endocarditis

Systemic	Cardiac
Systemic lupus erythematosus	Atrial myxoma
Antiphospholipid syndrome	Other cardiac neoplasms
Lyme disease	Libman–Sacks endocarditis
Reactive arthritis	
Polymyalgia rheumatica	
Swine flu[18]	

Box 1 Modified Duke criteria

Major criteria

Positive blood culture with typical infective endocarditis (IE) micro-organism, defined as one of the following:

1. Typical micro-organism consistent with IE from two separate blood cultures:
   - Viridans-group streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, community-acquired Enterococci, in the absence of a primary focus, or
2. Micro-organisms consistent with IE from persistently positive blood cultures defined as:
   - At least two positive cultures of blood samples drawn >12 h apart, or
   - All three or a majority of four separate cultures of blood (with first and last sample drawn 1 h apart).
   - *Coxiella burnetii* detected by at least one positive blood culture or IgG antibody titre for Q fever phase 1 antigen >1:800.

Evidence of endocardial involvement with positive echocardiogram defined as:

- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
- Abscess, or
- New partial dehiscence of prosthetic valve or
- New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).

Minor criteria

- Predisposing factor: known cardiac lesion, recreational drug injection.
- Fever >38°C.
- Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, Janeway lesions, conjunctival haemorrhage.
- Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor.
- Microbiologic evidence: positive blood culture but not meeting a major criterion as noted previously* or serological evidence of infection with organism consistent with IE but not satisfying major criterion.

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

suspected IE to identify vegetations, characterise the haemodynamic severity of valvular lesions, assess ventricular function and pulmonary pressures and detect complications.

TTE has a sensitivity of between 50% and 90% and a specificity >90% for detection of vegetations in NVE. However, the sensitivity of TTE is lower in patients with prosthetic valves or intracardiac devices.[19] TOE is recommended in patients in whom there is a clinical suspicion of IE where TTE is non-diagnostic, to assess for complications or when intracardiac device leads are present.[19]

Proving an infectious agent in the blood or on the valve is the second essential criterion in the diagnosis of IE. The gold standard in diagnosis is pathological examination of resected valve or embolic fragments.[20] In their 2014 guidance The ACC and AHA state that three sets of blood cultures should be taken, 6 h apart, at separate sites prior to commencing antibiotics in patients with a chronic or subacute presentation of IE. However, it is recognised that this is not always appropriate, especially in the acutely unwell septic patient; thus, their recommendation is that at least two sets of blood cultures should be taken in patients at risk of IE with an unexplained and prolonged (over 48 h) fever.[19] The 2015 European Society of Cardiology (ESC) guidelines regarding blood cultures are similar but have a notable difference; they suggest that the time interval between the three sets of blood cultures should be 30 min.[20] These guidelines go on to state that bacteraemia in IE is almost constant and thus the rationale for timing blood cultures with spikes of temperature is flawed.

There is minimal benefit in attaining more than three sets of blood cultures as up to 95% of cases of IE will be blood culture positive after 7 days.[21] Antibiotics received before blood cultures are the major cause of blood-culture-negative IE, which occurs in up to 31% if cases of IE, and thus should be avoided if possible.[20] The ESC identifies fungi and fastidious bacteria as other possible causes for blood-culture-negative IE and recommends consultation with a microbiologist and specialist culture techniques in these instances[20] In some settings, it is appropriate to withhold antibiotics until the initial blood culture results are known, for instance in subacute IE in the absence of severe illness. The importance of early blood cultures as part of the management and diagnosis of IE cannot be overstated.

Other investigations are useful in evaluating the clinical manifestations of IE, namely the embolic phenomena arising from right-sided IE. In the IVDU patient the most pertinent investigations would be imaging of the chest via simple radiograph or CT. These techniques are able to demonstrate septic pulmonary emboli, which may be seen in the form of a cavitating lung lesion (figure 3). Sequelae of these embolic events are also widely seen in the form of pneumonia and pleural effusions.

Further appropriate imaging modalities should be tailored to the patient's symptoms, signs and clinical examination findings. For instance, the patient with back pain or abdominal pain may benefit from a spinal MRI or abdominal CT, respectively, which have the capacity to assess for metastatic infection or systemic emboli. The literature, a prospective study of 130 patients from 2010, also reports the values of imaging the brain routinely in suspected IE leading to one-third of *possible* IE becoming *definite* based on the evidence of septic emboli on brain MRI.[22] It is less clear whether MRI would be of benefit in right-sided IE, given that in this study MRI was positive in only 3 of the 10 patients with right-sided endocarditis; two of these three were later found to have a patent foramen ovale.

The ECG can also be useful in evaluating clinical manifestations of IE, particularly periannular extension of IE for example, aortic root abscess, a complication seen more commonly in active IVDUs[23] (figure 2). This manifests as new widening of the PR interval suggesting a new atrioventricular conduction defect.[24]

Laboratory investigations other than blood cultures are non-specific but may aid in raising the clinical suspicion of IE or in the workup of the patient. Elevated inflammatory markers (C reactive protein, erythrocyte sedimentation rate and leucocytosis) and a normochromic normocytic anaemia are usually present in endocarditis.[1] Urinalysis may reveal pyuria, proteinuria, haematuria or red cell casts, which indicate glomerulonephritis (a minor diagnostic criterion).

Opportunistic screening of other conditions in IVDUs should not be overlooked. The high incidence of HIV in IVDUs presenting with IE has already been discussed and the assessment of any IVDU patient should include screening for other blood-borne viruses including hepatitis B and C, where appropriate.

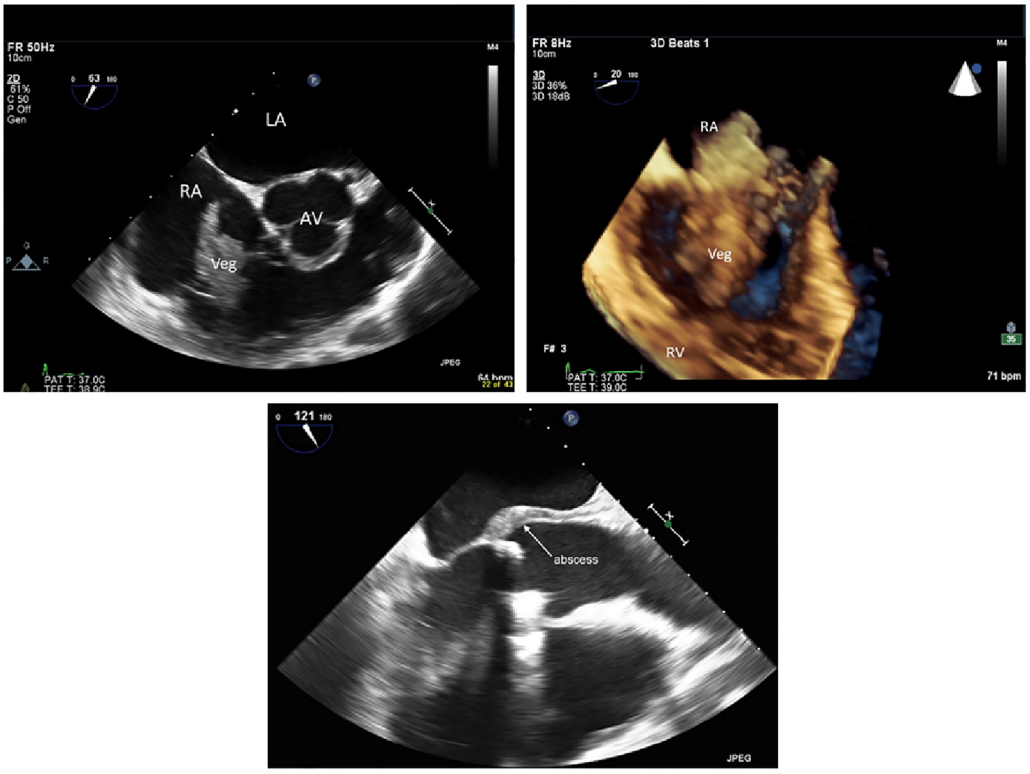

Figure 2 Echocardiograms with typical infective endocarditis (IE) vegetations. Top left: trans-oesophageal echocardiogram showing a typical tricuspid vegetation (Veg). Also shown: left atrium (LA), right atrium (RA) and aortic valve (AV). Top right: a three-dimensional echocardiogram showing a similar tricuspid vegetation (Veg). Also shown: right atrium (RA) and right ventricle (RV). Bottom: echocardiogram showing an aortic root abscess.

TREATMENT

Managing IE centres around two key principles: Eradication of the infective agent in the vegetation and reversal (or minimisation) of intracardiac and systemic consequences of the infection. Therefore, the pragmatic approach to treatment focuses initially on empirical and, later, targeted antibiotic therapy and occasionally the need to operate. However, there are some inherent challenges faced by the clinician treating IVDUs, which must be taken into account including use of long-term intravenous catheters, social issues, compliance and risk of continued intravenous drug misuse.

The choice of antibiotic has been extensively studied and warrants careful consideration. The initial antibiotic choice should

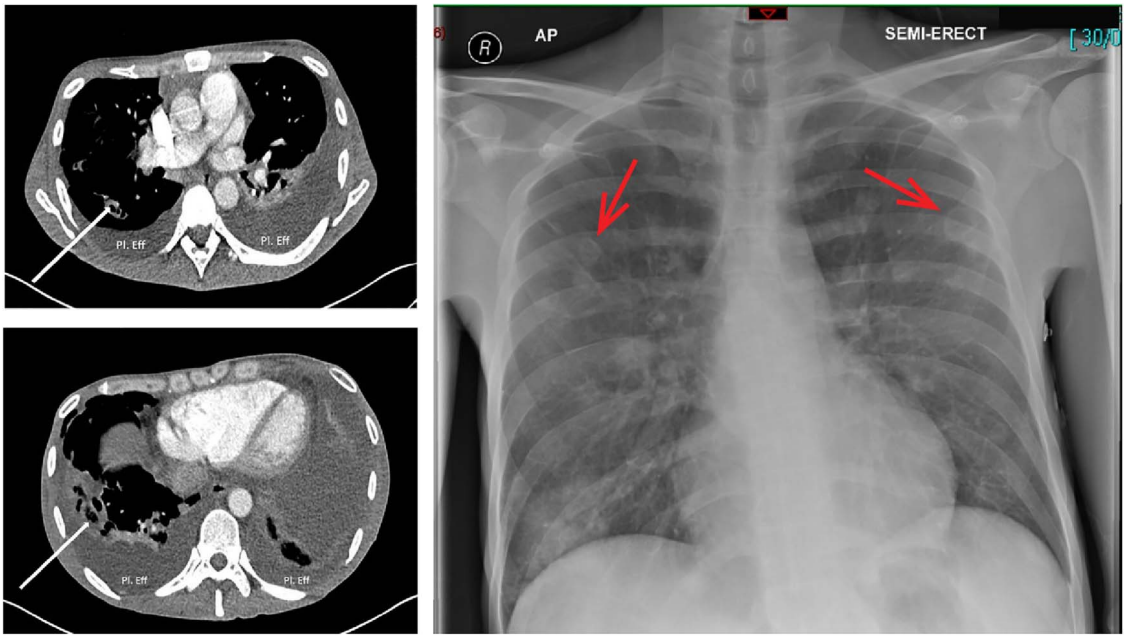

Figure 3 Chest imaging demonstrating septic pulmonary emboli. Top: CT chest showing cavitating lung lesion (arrow) and bilateral pleural effusions. Bottom: CT chest showing a lung abscess (arrow) and bilateral pleural effusions. Right: Chest X-ray showing cavitating lesions bilaterally (arrows).

be governed by the locations of the vegetation, the suspected pathogen and may also be affected by the type of drug the IVDU uses. The ESC recommends the following for right-sided endocarditis.[20]

- *S. aureus* should always be covered in right-sided IE with penicillinase-resistant penicillins, daptomycin or vancomycin depending on the local methicillin resistant staphylococcus aurerus (MRSA) prevalence, in addition to gentamicin.
- Antifungal treatment added if the patient uses brown heroin dissolved in lemon juice, to cover *Candida* spp.
- An antipseudomonas agent should be added if the patient is a pentazocine addict.

There is also emerging evidence that a 2-week regimen with oxacillin or cloxacillin may be used without the need for gentamicin in patients with no evidence of IE-related complications who are HIV negative, a small vegetation and a good initial response to treatment.[20] The advantages of a 2-week course are clear in increasing compliance and minimising hospital stays.

This is not always clinically appropriate and the ESC recommends the standard 4–6-week regimen in the following circumstances concerning right-sided IE:

- Slow clinical or microbiological response to antibiotics.
- The presence of complications (including: heart failure, vegetations >20 mm, acute respiratory failure, septic metastatic foci outside the lungs or extracardiac complications).
- Antibiotics other than penicillinase-resistant penicillins.
- IVDU with CD4 count <200 cells/μL (with or without AIDS).
- Associated left-sided IE.

The ESC also suggests an oral course of ciprofloxacin and rifampicin for IVDUs with right-sided IE due to *S. aureus* where the following criteria are met: the strain is fully susceptible to both drugs, the case is uncomplicated and patient compliance is carefully monitored.[20] Historically, IE in IVDUs has been difficult to treat with long-term intravenous antibiotics due to the potential misuse of the necessary intravenous systems needed by the patient, which makes this proposed oral course promising.

It should be noted that these are guidelines only and all clinicians should liaise with the local microbiology or infectious diseases department when treating IE. It is beyond the scope of this article to discuss all appropriate antibiotic/antifungal medications for the vast array of causative organisms in IE.

Cardiac surgery has an important role, primarily following failed medical therapy or as a matter of urgency in acute heart failure. But surgery has many risks and thus the decision to operate should include careful risk–benefit analysis. Generally, indications for surgical management of IE in IVDUs are similar to those in other patients, but due to the high recurrence rates of IE among IVDUs, a more conservative approach to surgery should be practised in these patients.

The AHA and ESC have both published guidelines to aid clinicians with this decision on when to operate in right-sided IE, which can be summarised as follows:[19 20]

1. Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy.
2. IE caused by organisms, which are difficult to eradicate (eg, persistent fungi), or bacteraemia for at least 7 days (eg, *S. aureus*, *P. aeruginosa*) despite adequate antimicrobial therapy.
3. Fever persisting despite 3 weeks of appropriate antibiotic treatment in the absence of a pulmonary abscess.
4. Tricuspid valve vegetations >20 mm, which persist after recurrent pulmonary emboli with or without concomitant right HF.

Main messages

- The majority of right-sided infective endocarditis (IE) is seen in drug misusers and the tricuspid valve is most commonly affected in intravenous drug users (IVDUs) with IE.
- *S. aureus* is the most frequently implicated pathogen.
- Presenting features of IE in IVDUs include constitutional features and, less commonly, sequelae of septic pulmonary embolisms.
- Blood cultures and echocardiogram are vital investigations in the diagnosis and management of IE.
- Treatment focuses on broad-spectrum antimicrobials followed by directed therapy based on sensitivities; there is a role for surgery in certain circumstances.
- Ethical and practical issues surround the treatment of an IVDU with IE and may affect success of treatment modalities, especially surgical.
- Recurrence of IE is high among IVDUs.

Current research questions

- What is the role of early versus delayed surgery to treat infective endocarditis (IE) in intravenous drug user (IVDU); particularly those with large vegetations or embolic events?
- How much, if any, does involvement in a rehabilitation programme following treatment reduce the risk of recurrence among the IVDU population?
- Short-term (2-week) antibiotic courses are now being used for the more simple cases. Is there scope for an intermediate-term (eg, 4-week) course rather than a 6-week course for more complex patients?
- What factors are responsible for a significant difference between short- and long-term mortality following surgery for IE in IVDUs compared with the general population? And, would improvements in social care post-discharge from hospital impact this?

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Self assessment questions

Answer true (T) or false (F) for the below:

1. With regard to the development of IE, which of the following are true?
   A. IVDU represents the largest risk factor in the development of IE.
   B. Iatrogenic causes are becoming less common.
   C. The predisposing factors have remained consistent over the past 50 years.
   D. Among IVDUs, males are more frequently affected compared with the general population.
   E. When compared with the general population, IVDUs develop IE at a younger age.
2. Which statements are correct about the aetiology of IE in IVDUs?
   A. IE in IVDUs tends to involve aortic valve.
   B. The most common infectious agent implicated in IE in both IVDUs and non-IVDUs is *S. aureus*.
   C. IVDUs are at higher risk of developing IE from relatively non-pathogenic bacteria.
   D. IVDUs are at higher risk of developing IE due to poor hygiene and non-sterile injection methods only.
   E. Polymicrobial IE is more common in IVDUs and is mostly due to combined enterococcal and streptococcal infection.
3. Which of the following about symptoms and signs of IE are true?
   A. IVDU patients typically display the peripheral stigmata of IE (Osler nodes, splinter haemorrhages, Roth spots).
   B. *S. aureus* endocarditis commonly has evidence of extracardiac infection.
   C. A tricuspid murmur is likely to be evident in tricuspid endocarditis.
   D. Symptoms of IE remain relatively consistent despite the site and nature of the infection.
   E. A new or changing murmur is more associated with left-sided IE rather than right-sided.
4. In diagnosing IE, which of the following are true?
   A. Evidence of new valvular regurgitation on auscultation of heart sounds is a major criterion in the *Modified Duke Criteria*.
   B. Prosthetic valves or intracardiac devices reduce the sensitivity of TTE in diagnosis of IE.
   C. All minor criteria (of the *Modified Duke Criteria)* need to be met to confirm diagnosis if no major criteria are met.
   D. Imaging (eg, MRI or CT) to search for metastatic is mandatory once IE is suspected.
   E. ACC and AHA guidance is to take three sets of blood cultures, at separate sites, 6 h apart prior to starting antibiotics in subacute IE.
5. In the treatment of IE in the IVDU population, which of the following are correct?
   A. Persistent fever in right-sided IE may be an indication for surgical intervention.
   B. It is never appropriate to start antibiotics before sufficient blood cultures are obtained.
   C. A relatively short, 2-week course of antibiotics can be used in certain circumstances.
   D. Following treatment, the risk of recurrence among IVDUs is low.
   E. Mortality rates are similar between IVDUs and non-IVDUs that have undergone surgery for IE.

These are not specific to IVDU patients and thus other factors need to be considered. For instance, it is usually not advised to operate on a patient who is unwilling to give up intravenous drug misuse or participate in a drug rehabilitation programme.

The choice of surgery in tricuspid IE should follow the principles of removal of vegetation (*vegectomy)* and debridement of surrounding area, and repair of the valve avoiding prosthesis if possible. Valve replacement is sometimes necessary.

A separate set of guidelines exist for IE affecting the left side of the heart.[19 20]

PROGNOSIS

The absolute mortality of IE is difficult to find in the literature. Estimates range from an in-hospital mortality of 5%–9% in right-sided native valve IE in IVDU[25 26] to an in-hospital mortality rate of 15% to 20% and a 1-year mortality rate nearing 40% for all populations with IE.[17]

Tricuspid IE has a lower mortality than other forms of IE.[27] Factors associated with a worse prognosis include left-sided IE, larger vegetation size and MRSA, fungal or polymicrobial aetiology.[8 28 29]

Evidence has shown that surgery for IE in IVDUs is associated with poorer long-term outcomes. Rabkin *et al*[30] compared short-term and long-term mortality following surgery in patients who were IVDUs and non-addicts. They found that short-term (30 days) mortality was almost equal, but longer-term (1, 5 and 10 years) was significantly worse among IVDUs.

Recurrence of infection remains a large problem when treating IE in IVDUs mainly due to the continued use of illicit drugs in these patients. In fact, intravenous drug misuse is the single largest risk factor predisposing to recurrent IE.[1] This illustrates the need to attempt to clarify future behaviours before deciding to operate.

CONCLUSION

In recent decades there has been a marked shift in the risk factors for IE with intravenous drug use representing the single largest predisposing factor in right-sided IE.

Clinicians must maintain a high clinical suspicion in the diagnosis of IE in IVDUs due to the diverse presentation and presence of comorbidities suppressing the host's immune response.

IE should be viewed as a spectrum of conditions whose manifestations and treatment options depend on a multitude of factors; from the physical site and nature of the valve involved, to the behavioural and social aspects of the patient, which are fundamental in the management of the intravenous drug misuser.

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Answers

1. A: T, B: F, C: F, D: T, E: T
2. A: F, B: T, C: T, D: F, E: F
3. A: F, B: T, C: F, D: F, E: T
4. A: F, B: T, C: T, D: F, E: T
5. A: T, B: F, C: T, D: F, E: F