

Infective endocarditis secondary to intravenous Subutex abuse

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ABSTRACT

Introduction: Subutex (buprenorphine) was approved by the Health Science Authority of Singapore for heroin detoxification in 2002. The number of heroin addicts has decreased in Singapore since the introduction of Subutex. However, Subutex abuse and its associated complications became arising medical problems. We report the management of a series of infective endocarditis cases secondary to Subutex abuse.

Methods: We identified 12 cases of infective endocarditis in former heroin addicts treated with Subutex from August 2005 to April 2006. All patients were interviewed by the research coordinator and prospectively followed-up for two years.

Results: The treatment period of Subutex endocarditis was often prolonged with a mean hospitalisation stay of 48 days, with 3.8 days in the intensive care unit. Multiple medical complications were noted. *Staphylococcus aureus* septicaemia accounted for 92 percent of cases. Mortality rate was 42 percent. Failure rate of medical therapy alone was common. 25 percent underwent open heart valve surgery. All patients were subsidised. Mean hospitalisation expenses was S\$31,218.

Conclusion: Subutex endocarditis causes significant morbidity and mortality. It imposes a heavy medical and financial burden to the patient and society. Multidisciplinary treatment involving cardiologists, infectious disease physicians, psychiatrists, surgeons, medical counsellors and social workers is required to manage these patients.

Keywords: buprenorphine, drug abuse complication, endocarditis, heart infection, infective endocarditis, Subutex

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INTRODUCTION

Subutex (buprenorphine) is a partial opioid agonist. It is indicated for substitution treatment in opioid drug dependent adults. Patients that are prescribed Subutex should be carefully monitored within a framework of medical, social, and psychological support as part of a comprehensive opioid-dependence treatment programme. The efficacy and safety of Subutex has been demonstrated in clinical trials.^(1,2) All trials used Subutex in conjunction with psychosocial counselling and a comprehensive addiction treatment programme. Subutex was demonstrated to be effective in reducing both the number of opiate positive urine samples and in retaining patients in treatment.

Subutex is safe when taken sublingually. However, there have been recent reports of Subutex abuse and various related medical complications. There have been local reports of intravenous abuse of Subutex,⁽³⁾ particularly in combination with benzodiazepines, such as Dormicum (midazolam). Cazorla et al published a case series on Subutex abuse.⁽⁴⁾ The documented complications are infectious endocarditis, cutaneous abscess, osteoarticular infections, meningitis and retinitis. There is little published literature on Subutex abuse-related endocarditis. We managed a number of patients diagnosed with infective endocarditis secondary to Subutex abuse. We aimed to describe the clinical presentations and outcomes of this unique type of drug abuse endocarditis.

METHODS

We report 12 cases of infective endocarditis secondary to Subutex abuse in a university hospital from August 2005 to April 2006. We followed-up these patients prospectively over a two-year period. All patients were interviewed by dedicated clinical coordinators. We reported the clinical presentations, complications and clinical outcomes at the end of two years.

RESULTS

The synopses of 12 cases of Subutex endocarditis are summarised in Table I. Patient 1 was a 28-year-old woman who had been abusing Subutex and Dormicum for three months. She presented with pneumonia and septic shock.

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Table I. Baseline demographics and clinical outcome at two-year follow-up.

Patient	Gender	Age (years)	Race	Occupation	Other drugs abused	Blood culture	Culture sensitivity	Valve involved	Other major complications	Two-year clinical outcome
1	F	28	Malay	Hairdresser	Dormicum	<i>S. aureus</i>	s: cloxacillin r: penicillin	TV	Lung abscess Renal embolisation DIVC Cardiomyopathy LVEF 25%	Recovered LVEF improved to 55%
2	M	45	Malay	Shipyards worker	Valium	<i>S. aureus</i>	s: cloxacillin	MV	Hepatitis C Anti-HCV riba positive Left finger gangrene LVEF 60%	Recovered
3	M	36	Malay	Car mechanic	Dormicum	<i>S. aureus</i>	s: penicillin cloxacillin clindamycin	TV	Melioidosis serology +ve, Hepatitis C anti-HCV riba positive Pulmonary septic emboli LVEF 55%	Absconded
4	M	30	Malay	Cleaner	Dormicum	<i>S. aureus</i>	s: cloxacillin gentamicin r: penicillin	TV/MV	Kidney abscess Hepatitis C Pulmonary abscess LVEF 60%	Recurrence of endocarditis Tricuspid valve perforation
5	M	35	Malay	Construction worker	Dormicum	<i>S. aureus</i>	s: cloxacillin r: penicillin	TV	Discitis Pulmonary septic emboli <i>S. aureus</i> pneumonia Hepatitis C Multiresistant <i>Klebsiella</i> UTI LVEF 35%	Recovered
6	M	49	Eurasian	Unemployed	Dormicum	MRSA	s: vancomycin gentamicin r: penicillin cloxacillin	TV	Lung abscess DIVC Discitis LVEF 65%	Bioprosthetic tricuspid valve replacement Recurrence of prosthetic valve endocarditis Death
7	M	31	Malay	Illegal VCD seller	Dormicum	<i>Streptococcus mitis</i> , <i>Prevotella</i> spp, <i>Acinetobacter</i> spp, <i>Aerococcus viridans</i>	s: penicillin ampicillin clindamycin	TV	Brain abscess Hepatitis C LVEF 65%	Absconded
8	M	25	Malay	House mover	Dormicum	<i>S. aureus</i> , <i>Pseudomonas</i> spp, <i>Acinetobacter baumannii</i>	s: penicillin gentamicin cloxacillin s: amikacin imipenem r: gentamicin penicillin	TV/MV	Septic shock Pulmonary abscess Brain septic emboli LVEF 58%	Prosthetic mitral valve replacement and tricuspid valve annuloplasty Death from intracranial haemorrhage
9	M	22	Malay	Petrol station assistant	Dormicum	<i>S. aureus</i>	S: cloxacillin gentamicin r: penicillin	TV	Lung abscess Hepatitis C Acute renal tubular necrosis Cerebral abscess LVEF 45%	Recurrent endocarditis Death
10	M	35	Indian	Unemployed	Dormicum	<i>S. aureus</i> , <i>Corynebacterium</i>	s: cloxacillin penicillin	AV	Brain abscess DIVC Heart failure from acute aortic regurgitation <i>Klebsiella</i> UTI LVEF 50%	Prosthetic aortic valve replacement. Prosthetic valve endocarditis Death
11	M	24	Malay	Unemployed	Dormicum	<i>S. aureus</i>	s: penicillin cloxacillin	TV	Septic shock DIVC Hepatitis C LVEF 50%	Death
12	F	23	Malay	Shop assistant	Dormicum	<i>S. aureus</i>	s: cloxacillin r: penicillin	TV	Lung abscess Renal emboli LVEF 63%	Recovered

S. aureus: *Staphylococcus aureus*; DIVC: disseminated intravascular coagulation; TV: tricuspid valve; MV: mitral valve; AV: aortic valve; LVEF: left ventricular ejection fraction; s: sensitive; r: resistant; UTI: urinary tract infection.

She developed multiple pulmonary septic emboli (Fig. 1). Echocardiogram showed large tricuspid vegetation. Blood culture grew *Staphylococcus aureus*. She was treated with two weeks of intravenous (IV) gentamycin and eight weeks of IV cloxacillin. Despite completing

the antibiotic regimen, she continued to experience septic symptoms. Repeat echocardiogram showed an impaired left ventricular systolic function, persistent vegetation and severe tricuspid valve destruction with resultant severe regurgitation. She underwent surgical vegetation excision



Fig. 1 Axial CT image of the thorax shows the bilateral pulmonary empyemas in a 28-year-old woman (patient 1) who had developed pneumonia and septic shock.



Fig. 2 Photograph shows the gangrenous left hand secondary to acute ischaemia in a 45-year-old man (patient 2) who developed acute left brachial artery thrombosis at the injection site.

and tricuspid valve replacement. She recovered after three months of hospitalisation.

Patient 2 was a 45-year-old man who had been abusing Subutex for six months. He injected Subutex powder into his arm veins in order to seek “a high”. He was admitted to the vascular surgery unit for acute left arm ischaemia secondary to brachial artery thrombosis after Subutex injection (Fig. 2). He was found to have heart murmur and persistent fever for one week. Echocardiogram showed tricuspid valve vegetation. Blood culture grew *Staphylococcus aureus*. He was treated with two weeks of low molecular weight heparin (Clexane) for the upper limb ischaemia and six weeks of IV cloxacillin. He recovered from the illness without surgical intervention for the arm ischaemia.

Patient 3 was a 36-year-old man who had been injecting Subutex, and occasionally Dormicum, for one year. He presented with symptoms of fever, chills, rigors and weight loss for one month. A diagnosis of pyrexia of unknown origin (PUO) was made. Blood culture grew *Staphylococcus aureus*. Echocardiogram showed tricuspid valve vegetation. He was treated with IV cloxacillin and gentamycin for two weeks and further cloxacillin for a total of six weeks. He absconded from the hospital after being found guilty for injecting diazepam (Valium) powder in the ward.

Patient 4 was a 30-year-old man who bought and sold Subutex on the black market. This trade brought him extra money. He had been abusing Subutex for two years. He cut the 8 mg Subutex tablet into four portions and injected the crushed powder intravenously after mixing it with water. He was admitted for sepsis. He developed infective endocarditis involving both the mitral and tricuspid valves (Figs. 3a–c). There was no patent foramen ovale demonstrated in the echocardiogram. He had

pulmonary septic emboli and disseminated intravascular coagulation (DIVC). He was treated with IV cloxacillin and IV gentamicin. Concurrently, he developed hepatitis C glomerulonephritis. He underwent a total of 60 days of IV antibiotic treatment in the hospital. He recovered from infective endocarditis, with residual tricuspid valve perforation and severe regurgitation.

Patient 5 was a 35-year-old man who was admitted to medical intensive care unit (MICU) for severe septic shock secondary to pneumonia and empyema. He had severe jaundice and was found positive for hepatitis C serology. Echocardiography showed vegetation in the tricuspid valves. Blood culture grew *Staphylococcus aureus*. He was treated with IV gentamicin and cloxacillin. Oral rifampicin was added on two weeks later. He required chest tube insertion for empyema drainage. He complained of severe low back pain. Magnetic resonance (MR) imaging of the spine showed discitis secondary to septic emboli (Fig. 4). He developed a few delirium episodes secondary to drug abuse in the ward. He received IV antibiotics for a total of 88 days and recovered from the illness.

Patient 6 was a 49-year-old man who had been abusing Subutex and Dormicum for two years. He was admitted for sepsis with PUO. Echocardiogram showed large tricuspid valve vegetation (Figs. 5a–c). Blood culture grew *Staphylococcus aureus*. He continued to have fever and chills. Subsequent blood culture grew Methicillin-resistant *Staphylococcus aureus* (MRSA). After interrogation, he admitted injecting Subutex in the ward. He developed hospital-acquired MRSA septicaemia. He was treated with four weeks of IV vancomycin and oral rifampicin but without success. He underwent tricuspid valve excision and bioprosthetic valve replacement. He was also a hepatitis C carrier. He continued to abuse Subutex post discharge. Two months later, he was admitted

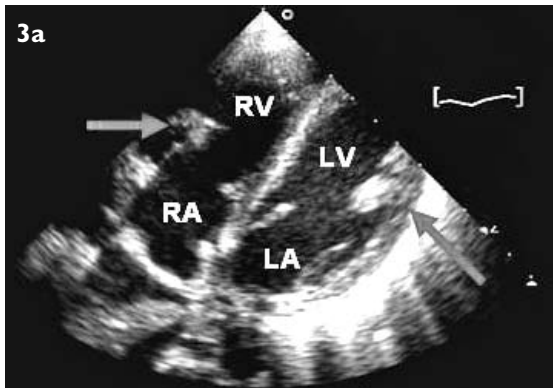


Fig. 3(a) Transthoracic echocardiogram (modified apical four-chamber view) shows valvular vegetations (arrows) in a 30-year-old man (patient 4) who developed endocarditis involving both the mitral and tricuspid valves.

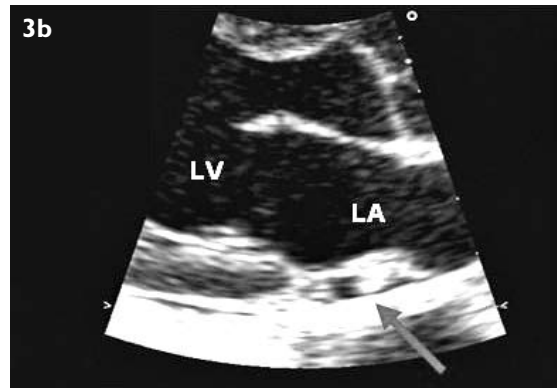


Fig. 3(b) Transthoracic echocardiogram (parasternal long view) shows posterior mitral valve vegetation (arrow).



Fig. 3(c) Transthoracic echocardiogram (parasternal long view) shows mitral valve regurgitation (arrow).

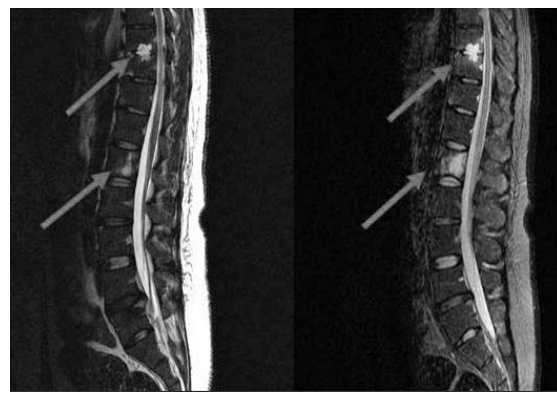


Fig. 4 Sagittal T2-W (left) and STIR (right) MR images show spinal abscess/discitis (arrows) in a 35-year-old man (patient 5) who presented with back pain.

to the orthopaedic unit presenting with severe low back pain. MR imaging of the spine showed discitis. Blood culture grew MRSA colony. Repeat echocardiogram showed very large vegetation on the prosthetic tricuspid valves with significant obstruction. He was given another course of IV vancomycin, gentamycin, clindamycin and oral rifampicin. He failed to respond to the medical therapy and developed heart failure and septic shock. He underwent open heart vegetation excision (Figs. 5d–f), and died two days postoperation.

Patient 7 was a 31-year-old man who had been abusing Subutex and Dormicum for two years. He presented with an altered mental status. He was diagnosed to have septic encephalopathy secondary to multiple brain septic emboli (Fig. 6). His blood culture grew group G *Streptococcus viridans*. His long line tip culture grew *Acinetobacter baumannii*. He had positive toxoplasmosis antibodies and positive hepatitis C serology. Echocardiogram showed tricuspid valve vegetations and large abscess cavity. He developed septic shock with DIVC. He required inotropic support, and was treated with IV penicillin and gentamycin for four weeks. The patient then absconded from the

hospital, and returned eight months later, presenting with persistent fever and chills. He continued to inject himself with Subutex and shared needles with other addicts. He had recurrent tricuspid valve endocarditis with multiple organisms isolated from the blood cultures that included *Streptococcus mitis*, *Prevotella* spp. and *Acinetobacter* spp. He was found stealing needles and injecting himself in the ward. He absconded from hospital after five weeks of antibiotics treatment.

Patient 8 was a 25-year-old man who abused Subutex for a few months. He presented with fever, breathlessness and lower limb swelling. Blood culture grew *Pseudomonas* spp. and *Staphylococcus aureus*. Echocardiogram showed mitral valve and tricuspid valve vegetations. Computed tomography of the thorax showed multiple pulmonary septic emboli. He was treated with IV cloxacillin, gentamycin and rifampicin. He failed to improve after antibiotic therapy and developed haemodynamic compromise after development of acute severe mitral regurgitation due to chordal rupture. He underwent emergency mitral valve replacement surgery and tricuspid vegetation debridement. He was treated with

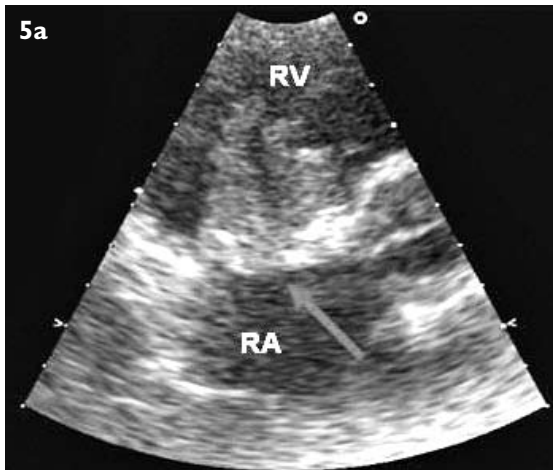


Fig. 5(a) Transthoracic echocardiogram (right ventricular inflow view) shows a large vegetation on the prosthetic tricuspid valve (arrow) in a 49-year-old man (patient 6) who presented with tricuspid prosthetic valve endocarditis.

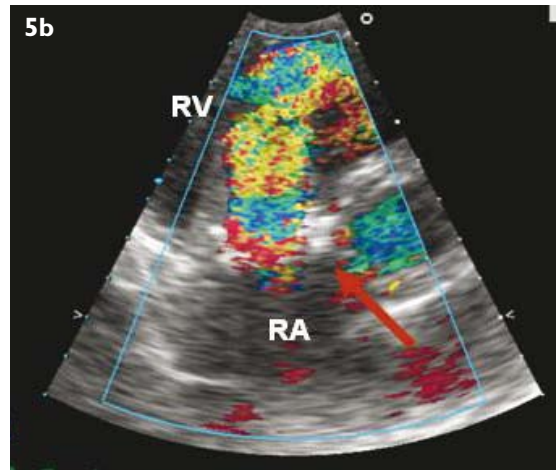


Fig. 5(b) Transthoracic echocardiogram (colour Doppler) of the right ventricular inflow view shows turbulence across the prosthetic tricuspid valve (arrow).

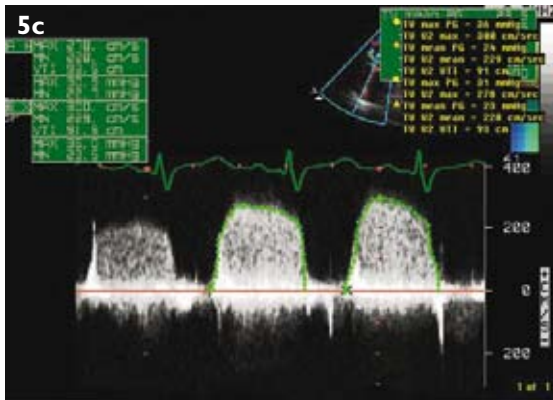


Fig. 5(c) Transthoracic echocardiogram (continuous wave Doppler) across the prosthetic tricuspid valve shows mean pressure gradient > 20 mmHg, which was consistent with severe tricuspid valve obstruction.

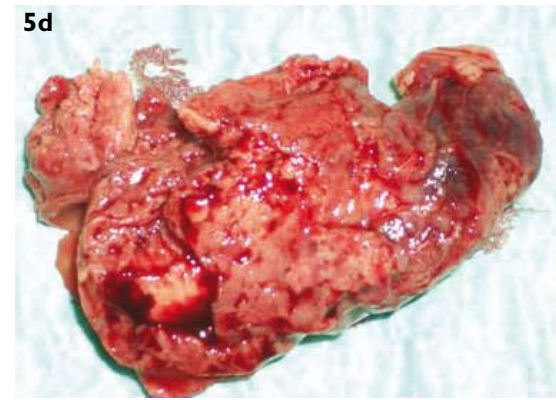


Fig. 5(d) Photograph shows the excised tricuspid valve vegetation measuring 35 mm x 19 mm.

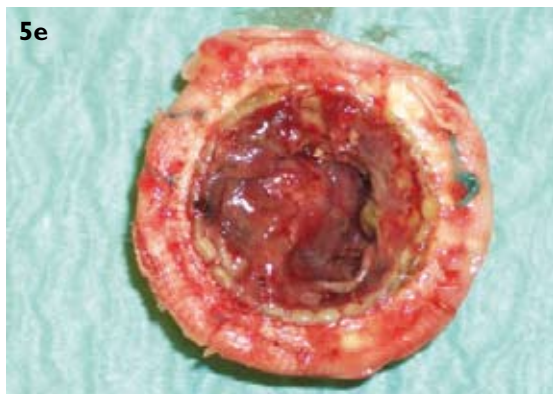


Fig. 5(e) Photograph shows the infected prosthetic tricuspid valve ring with abscess.

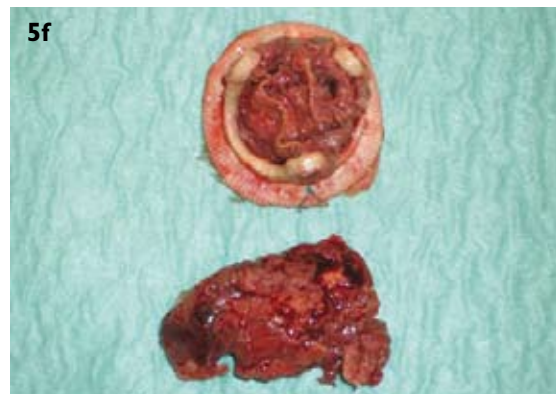


Fig. 5(f) Photograph shows the excised prosthetic tricuspid valve and large vegetation.

a prolonged course of IV antibiotics and stayed in hospital for six months. He recovered after surgery. Unfortunately, he was readmitted 12 months later for severe spontaneous intracranial haemorrhage due to warfarin over-anticoagulation. He died during that admission.

Patient 9 was a 22-year-old man who abused both

Subutex and Dormicum. He presented with prolonged fever. Echocardiogram showed large tricuspid valve vegetation. He was treated with IV cloxacillin after identification of positive *Staphylococcus aureus* growth on blood culture. He was non-compliant with treatment. He discharged himself against medical advice three

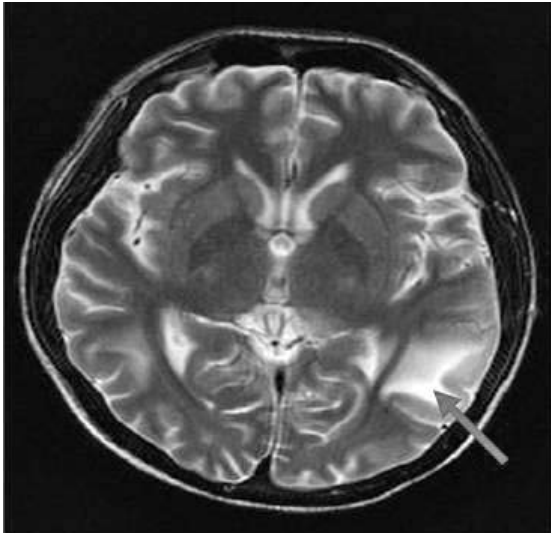


Fig. 6 Axial T1-W MR image shows a large left cerebral abscess (arrow) in the brain of a 31-year-old man (patient 7) who presented with septic encephalopathy.

times during the entire treatment period. His condition deteriorated. Echocardiogram one month later showed multiple enlarging tricuspid valve vegetations, severe tricuspid regurgitation, and impaired left ventricular ejection fraction from 65% to 45%. He developed pulmonary septic embolic, septic shock, brain abscess, seizures and kidney abscess. He was infected with hepatitis C, and developed hepatitis C-associated mesangial proliferative glomerulonephritis. Patient died from septic shock and multiorgan failure.

Patient 10 was a 35-year-old man who had a history of congenital bicuspid aortic valve with moderate aortic regurgitation. He had been abusing Subutex for months, despite warnings given by doctors regarding the high risk of infective endocarditis. He presented with fever, confusion and right hemiparesis for three days. He developed severe septic shock with multiple brain septic emboli. He was intubated and managed in the intensive care unit. He developed acute heart and renal failures. Transoesophageal echocardiogram revealed large aortic valve vegetations with severe aortic regurgitation (Figs. 7a–c). Blood culture grew *Staphylococcus aureus* and *Corynebacterium* spp. He underwent emergency aortic valve excision and replacement (Fig. 7d). He recovered from the infection, and had a fairly good functional return after two months of outpatient rehabilitation. Unfortunately, he continued to abuse Subutex and was readmitted 18 months later for prosthetic valve endocarditis and septic shock. He underwent prosthetic valve excision and died during the admission.

Patient 11 was a 24-year-old man who had been abusing Subutex for three months. He developed prolonged

Table II. Complications of infective endocarditis secondary to Subutex abuse.

Complication	No. (%) (n = 12)
Tricuspid valve vegetation	11 (92)
Staphylococci septicaemia	11 (92)
Pulmonary emboli / abscess	9 (75)
DIVC / septic shock	9 (75)
Hepatitis C	6 (50)
Brain abscess	4 (33)
Renal abscess	4 (33)
Mitral valve vegetation	3 (25)
Death	5 (42)
Discitis	2 (16)
Hepatitis B	1 (8)

Table III. Length of hospitalisation and bill amount in Singapore dollars.

Patient	Ward stay (days)	ICU stay (days)	Hospital bill (\$)
1	83	7	60,676
2	26	4	20,022
3	28	3	17,443
4	60	0	27,178
5	82	2	43,800
6	27	10	49,663
7	44	0	30,053
8	47	0	20,004
9	8	4	15,351
10	78	10	61,500
11	0	6	10,600
12	46	0	18,330
	44.2*	3.8*	374,620†

* mean no. of days

† total bill amount

fever and chills for one month. He did not seek medical treatment. He was found collapsed at home by family members. He was intubated at the emergency department and transferred to the MICU. He presented with severe septic shock. His temperature was 41°C and blood pressure was 80/60 mmHg. Clinical examination revealed Osler's nodes, splinter haemorrhage and a loud pansystolic murmur. Echocardiogram revealed large tricuspid valve vegetations. Blood culture grew *Staphylococcus aureus*. He was treated with IV cloxacillin and gentamycin, and later on converted to vancomycin and imipenem. He was given inotropic support with an intraaortic balloon counterpulsation pump. Despite intensive treatment, he continued to deteriorate and died on the fourth day after admission.

Patient 12 was a 23-year-old woman who had learnt to inject Subutex from her friends and had been abusing Subutex for three months. She presented with fever, chills and rigors for three weeks' duration. Chest radiograph showed multiple pulmonary consolidations and abscess cavities. Echocardiogram showed tricuspid

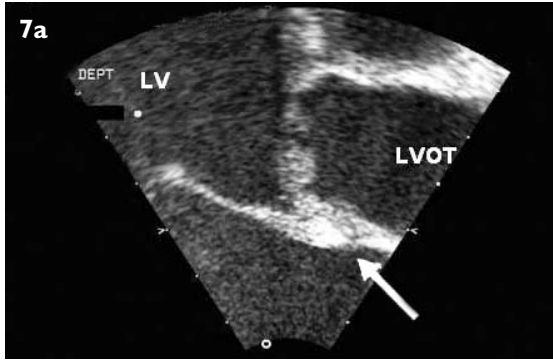


Fig. 7(a) Transoesophageal echocardiogram (aortic valve long-axis view) shows vegetations on the bicuspid aortic valve (arrow) of a 35-year-old man (patient 10) with congenital bicuspid aortic valve and who developed aortic valve endocarditis.

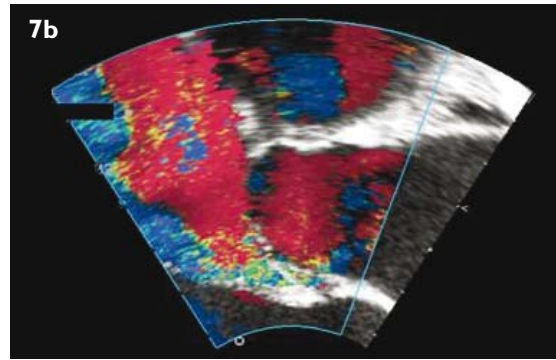


Fig. 7(b) Transoesophageal echocardiogram (colour Doppler of aortic valve long-axis view) shows severe eccentric aortic regurgitation.



Fig. 7(c) Transoesophageal echocardiogram (aortic valve short-axis view) shows vegetations on the valve cusps (arrow) and periannular thickening.



Fig. 7(d) Photograph of the excised bicuspid aortic valves shows the large vegetations.

valve vegetation. Blood culture grew *Staphylococcus aureus*. She recovered after treatment with six weeks of IV cloxacillin.

We interviewed the patients and identified some of the reasons for abusing Subutex via IV injection:

- (1) More rapid onset of action: euphoric response within 30 seconds with the IV route, compared to 10–20 minutes with the sublingual route.
- (2) False belief that IV Subutex can enhance erection and sexual function.
- (3) Combination usage with benzodiazepines, especially Dormicum and Erimin (Nimetazepam) in order to enhance euphoric effect.
- (4) Psychological addiction to the habit of injecting drugs: habitual injection abuser.
- (5) Peer pressure: especially among the Malay drug abusers. They tend to group together to inject drugs and share needles.
- (6) To reduce cost: injection route often requires a smaller dosage compared to the sublingual route.

Subutex tablets can be crushed into powder and dissolved in hot water. The insulin needle was used to inject the suspension into the veins of upper limbs.

Occasionally, the patients injected blood vessels in the groin (femoral arteries was referred as “the highway”) and neck. Few patients would clean the injection sites with soap and water.

DISCUSSION

IV drug abuse has been increasing worldwide in recent years. The World Health Organisation documented that in 1993, 80 countries reported the existence of injecting drug abuse. However, in 1999, this number increased to 136 countries.⁽⁵⁾ The increase was due to both an increase in the number of abusers and awareness of the issue. IV drug abuse results in introducing pathogens and other contaminants into the body. This is secondary to sharing needles and absence of sterile preparation and injection techniques. In addition, the injected drugs may not be pure: they may be mixed with substances, such as talc, lactate or quinine. Impure fake Subutex tablets may be purchased from illegal sources.

Subutex is a synthetic opiate and thus has euphoric effects sought by opiate abusers.⁽⁶⁾ Subutex, the form that does not contain naloxone, is more vulnerable to abuse because it can be crushed and injected without causing

withdrawal symptoms in the abuser. Although the US Food and Drug Administration (FDA) and Ministry of Health (MOH) Singapore recommend that physicians limit the use of Subutex to supervised administration sessions, this is not a mandated requirement. As a result, opportunities for Subutex abuse remain. Subutex has been prescribed legally for years in some overseas countries, where its diversion for illicit use has been reported.⁽⁷⁾

Subutex abuse had been reported in Singapore since early 2002. It had resulted in a number of complications and deaths.^(8,9) Instead of administering the medicine sublingually as prescribed, many drug addicts were abusing Subutex by dissolving it in hot water and injecting themselves with the suspension. The abusers might not have fully dissolved the drug, especially when it is mixed with other drugs like Dormicum or Erimin. This could result in acute thrombosis or arterial vasospasms, causing stroke or even death. Skin contamination during injections was a major risk of infection especially when needles were being reused.

The common presentations of the patients in our series were fever and chills from septicaemia. There were various other symptoms from systemic involvement (Table II), including cerebral abscess, pulmonary septic emboli, empyema, endocarditis, septic renal embolic and septic hepatitis. Viral infections could be spread by sharing of needles, such as HIV, and hepatitis B and C. The most common bacteraemia was caused by *Staphylococcus aureus*. However, other bacteria could be present due to multiple contaminated skin injections. These were *Streptococcus*, *Pseudomonas*, *Actinobacter* and Anaerobic species.

Compared to the previous published papers of infective endocarditis due to non-drug abuse causes,⁽¹⁰⁾ our series showed a higher inpatient mortality of 42% vs. 16%. Valve surgery was less likely to be performed in our series (25% vs. 49%). A possible explanation was that the surgeons were more reluctant to operate on these patients who had a high likelihood of recurrent drug abuse. There was fear of recurrent endocarditis of the prosthetic valves postoperation. Two of the three patients who underwent prosthetic valve replacement developed prosthetic valve endocarditis as a result of continuing drug abuse.

Compared to the literature on infective endocarditis secondary to IV heroin abuse (IVDU), the mortality rate in our series was higher, 42% vs. 10% and 16% in two reports.⁽¹¹⁻¹³⁾ The lower mortality of IV heroin endocarditis in previously-published reports was explained by younger aged patients with structurally normal hearts. In our report, the high mortality rate could

be explained by a delay in disease presentation, poor compliance to treatment, and continuing Subutex abuse during treatment. The similarities in our case series and other reported IVDU endocarditis series are a younger age group, a more common tricuspid valve involvement and a high prevalence of *Staphalococcus aureus* as the causative organism. Hepatitis C carrier status was found in 50% in our cohort, which is similar to that reported in the literature.⁽¹⁴⁾ The hepatitis B carrier rate, however, was lower in our series (8% vs. 44%). This could be explained by the nationwide immunisation programme locally.

Management of these patients required collaboration with the infectious disease physician, cardiologist, psychiatrist and cardiovascular surgeon. Counselling and financial support were important as most of these patients faced family, social and financial problems.^(15,16) Another problem encountered was the non-compliance issue; a few of the patients were found missing in the wards or wandering around in the hospital. We spotted visitors bringing in benzodiazepines and Subutex to these patients during hospitalisation. Several patients absconded from the hospital after having been found guilty for continual drug abuse in the wards. One measure which was used to monitor for inpatient drug abuse was by placing a special sticker seal onto the PICC line port; if the seal was broken, we knew that the patient could have attempted to inject drugs through the lines. It was not easy to discipline these patients in the normal hospital setting unless there were laws to constrain them in an isolation ward with perhaps police provided to enforce the treatment.

Drug abuse behaviour and dependence is a chronic illness; hence, it is a difficult task to simply persuade patients not to abuse drugs again. Counselling and psychosocial treatment are necessary in both the short and long term. Some patients (i.e. patient 6 who continued to inject drugs after valve surgery) may continue to abuse drugs and in whom early heart valve surgery may expose the prosthetic valves to a continuing threat of re-infection. Perhaps, we should set a higher threshold for early surgical intervention before these patients are determined to stop drug abuse. Another astonishing fact was the high hospitalisation costs (Table III). All patients were warded in the subsidised C class ward and received an 80% financial subsidy from the government. The mean hospitalisation bill was S\$31,218, and the mean hospitalisation stay was 48 days, with an average 3.8 days spent in the intensive care unit. This could have a significant impact on the public health system and resource allocation if Subutex endocarditis becomes more prevalent. It is therefore important to vigilantly monitor the situation.

Other pharmacological formulations to prevent drug abuse may be considered. Subuxone, a combination of Subutex and naloxone, when being injected into the blood, produces a much less euphoric effect. It can potentially reduce the tendency of abuse and drug diversion. A depot formulation of Subutex is currently being developed. This depot formulation is an injectable solution that contains tiny biodegradable capsules of Subutex. It can slowly release the drug over several weeks. This new formulation can be administered in a physician's office once every four to six weeks and could further safeguard against diversion by eliminating the need for patients to possess Subutex in the tablet form.

In conclusion, Subutex has been classified as a controlled drug in Singapore since August 2006. It can no longer be prescribed by general practitioners. The incidence of Subutex endocarditis has dropped since then. We found that Subutex endocarditis is difficult to treat and often needs a prolonged antibiotic course, intensive care and surgical intervention. It causes high mortality and morbidity. It also imposes a heavy toll to the financial resources of the institution.

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